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National Institute on Aging

Annual Report

October 1, 1981 through September 30, 1982

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NIA ANNUAL REPORT

TABLE OF CONTENTS

Office of the Director

Office of the Director OD-1
Information Office OD/IO-5

Report of Behavioral Sciences Research Program

Scope of the Program BSR-1
Program Goals BSR-1
Program Structure BSR-2
Current Program Activities BSR-4
Equal Employment Opportunities BSR-6
Evidence of Program Performance BSR-6
Scientific Accomplishments BSR-7

Report of Biomedical Research and Clinical Medicine Program

Program Description BRCM-1
Program Highlights BRCM-1

Report of Epidemiology, Demography, and Biometry Program

Overview of Epidemiology, Demography and Biometry Program . EDBP-1
Overview of Epidemiology Office EDBP-2
Overview of Demography and Economics Office EDBP-19
Overview of Biometry Office EDBP-25

Report of the Intramural Research Program (Gerontology Research Center)

Office of the Scientific Director GRC/OSD-1
Laboratory of Behavioral Sciences GRC/LBS-21
Laboratory of Molecular Aging GRC/LMA-35
Laboratory of Neurosciences GRC/LNS-48
Laboratory of Cellular and Molecular Biology GRC/LCMB-63
Clinical Physiology Branch GRC/CPB-72

Report of the Planning and Extramural Affairs Program

Planning and Evaluation Office OPEA-1
Scientific Review Office OPEA-2
Program Analysis and Technical Information Office . . . OPEA-2

OFFICE OF THE DIRECTOR

The NIA is now in its seventh year of operation and continues to make progress in conducting, supporting, and encouraging research on all facets of the aging process--biological, social, and behavioral. The Institute is faced with an ever-increasing number of topics to be addressed, from research in long-term care to the dementias of aging. Some of the specific areas of growth within the last year at the NIA include the following:

Program Announcements

In FY 82, the biomedical research and clinical medicine program (BRCM) issued an announcement in the area of pharmacology to encourage studies of drug responses in the elderly, to encourage studies to understand the mechanisms responsible for altered responses to drugs in the elderly, and to apply such information to improved treatment of diseases and disabilities in older people.

In FY 82, there was a continuation of the NIA Academic Award to recruit and prepare future academic investigators for careers in research and training, with special emphasis on geriatric medicine and related clinical disciplines. This institutional award, introduced in 1981, provides qualified candidates with an opportunity for five years of special study and supervised experience to further his/her individual needs. The Geriatric Medicine Award to establish geriatric medicine curriculum in medical schools and research in areas relevant to aging was continued in FY 82. A total of 26 awards are now supported. The small grant award program which provides support for pilot projects was established in FY 82 with the funding of 18 awards.

Teaching Nursing Home

In November, 1981 the Institute issued a program announcement on the establishment of research programs in nursing home settings in conjunction with university medical schools or medical centers. NIA proposed the creation of teaching nursing homes to help the Nation gear its biomedical and other research and training capacities to the long-term care needs of its elderly population. The NIA recommended that the public and private sectors form a partnership to develop teaching nursing homes in affiliation with universities, especially their medical, nursing, and social service schools.

The teaching nursing home will focus on such research issues as senile dementia, fecal and urinary incontinence, nutritional problems, drug interactions and behaviorial studies. Doctors, nurses, pharmacists, behavioral scientists, social workers, nurse aides, and physical, occupational, and speech therapists will have opportunities to work and learn collaboratively. The Institute has awarded its first two teaching nursing home grants to the Albert Einstein College of Medicine and the Philadelphia Geriatric Center (in collaboration with the Medical College of Pennsylvania and the University of Pennsylvania).

Airline Pilots Study

NIA was the lead NIH agency in a Congressionally mandated study of the effects of aging on airline pilot health and performance as a means of determining if mandatory retirement at age 60 is medically warranted. The report was submitted to Congress on October 2, 1981.

The report cited that in the absence of medical appraisal systems that can predict individual pilot health and performance, the present age limit should be retained. It proposed an approach that requires a program of medical and performance appraisal that could be applied on an individual basis to permit some pilots to continue flying to age 65.

The report also concluded that there is "no special medical significance to age 60--or to any other specific age--for mandatory retirement of airline pilots. Yet it found that "age-related changes in health and performance influence adversely the ability of increasing numbers of individuals to perform as pilots with the highest level of safety."

The report recommended "that the Federal Aviation Administration or some other appropriate Federal agency be requested to engage in a systematic program to collect the medical and performance data necessary to consider relaxation of the current age 60 rule." The panel also stated "that, in view of the growing importance of commuter air carriers, the present age limit be extended to cover all pilots engaged in carrying passengers for hire" in order to provide a level of safety equivalent to that of commercial air carrier operations.

White House Conference on Aging

The NIA assisted in the planning and operation of the White House Conference on Aging, which was held from November 29 to December 3, 1981. In addition, the Institute commissioned 36 scientific papers on various health topics for the conference, and NIA Information Office staff members perpared lay summaries of a number of these papers for distribution to conference delegates. The NIA displayed its own exhibit at the conference and helped coordinate an NIH-wide Health-Research Fair.

The NIA also prepared two progress reports--one on senile dementia of the Alzheimer's type (SDAT) and the other on geriatric medicine--as well as two shorter brochures entitled What is Aging Research? and What is Geriatric Medicine? for distribution at the conference.

Conferences and Workshops

Population Aging: Some Consequences for Social Institutions and Human Service Organizations

BSR sponsored this conference in May 1982 in cooperation with the American Council of Life Insurance. The purpose was to focus attention on population aging in the United States and to explore the impact of the most important and forseeable demographic trend in the next five decades.

Changing Work and Aging Workers

A series of workshops were sponsored by BSR in May and September 1982 to examine and clarify the nature of the interplay between changing work roles and aging workers. Additional follow-up meetings are planned for FY 83.

Independent Living in the Household

BSR sponsored a workshop in September 1982 to specify conditions that can sustain the health, well-being, and independence of the very old and to discuss means of reversing disabilities when they occur.

NIA Highlights

The Equal Employment Opportunity office of the NIA continued to play a very active and important role in the Institute. In January 1982, the EEO organized a meeting between NIA staff members and the staff of Provident Hospital, Baltimore, Maryland. The purpose of the meeting was to inform the medical staff of this black hospital about the small grant application and to assist the hospital in identifying areas in which they might consider research.

In February 1982, the EEO organized and presented NIA's first programs for GRC employees on Black History Month. In June 1982, NIA was represented at the first Public Health Service EEO Conference in Reston, Virginia. This conference was composed of some 300 national delegates. Topics of discussion included development of methods for recruiting minorities, identifying problems and opportunities for women and handicapped workers, and discussion of minority underrepresentation in the Federal government.

Dr. Daniel Cowell, formerly Special Assistant to the Director, was appointed NIA's Assistant Director for Health Promotion in June 1982. Dr. Cowell's duties include the following: developing and coordinating health promotion, disease prevention and technology transfer activities in behalf of the Institute; chairing the NIA Ad Hoc Interagency Committee on Research on Aging; and coordinating relevant NIA activities with agency representatives on that committee; and serving as the official liaison between the OD/NIA and the Administration on Aging (AoA). In addition, Dr. Cowell will be the NIA representative on the NIH OMAR Advisory Committee and the NIH Committee on Health Promotion and Disease Prevention.

In September 1982, NIA's first director, Dr. Robert Butler resigned to accept a position with the Mount Sinai School of Medicine of the City University of New York and The Mount Sinai Hospital, New York. As Chairman of the Gerald and May Ellen Ritter Department of Geriatrics and Adult Development of the Medical School, Dr. Butler is heading the country's first geriatric medicine department in a medical school. Dr. Butler is also Brookdale Professor of Geriatric and Adult Development of the Medical School and Director of the Gerald and May Ellen Ritter Department of Geriatrics and Adult Development of the Hospital.

Dr. Robert L. Ringler was appointed NIA Acting Director on July 26, 1982.

The NIA Laboratory of Neurosciences (LNS) clinical program admitted its first inpatients in September 1982. LNS, established in 1980, is involved in an intensive investigation of brain metabolism in relation to normal human aging and dementia.

Dr. Stanley I. Rapoport, LNS chief and Dr. Neal R. Cutler, chief of the newly instituted clinical program, together with a staff of research neurologists, psychologists, and other health professionals, have recently initiated a series of activities focusing primarily on the dementias and related neuropathologic disease of the elderly. Studies look closely at Alzheimer's disease, the most common form of senile dementia, and at multi-infarct dementia, which is caused by a series of minor strokes.

The clinical pharmacology of aging is another major area of interest for the NIA LNS clinical program. The focus of drug studies will be on how drugs are metabolized in the elderly versus the young adult, why the effectiveness of certain drugs seems to vary among brain regions, and how medical scientists can reach various brain regions with effective concentrations of drugs.

INFORMATION OFFICE

The combined effect of a formal moratorium on the printing of publications and an unofficial moratorium on the publication of press releases resulted in some significant changes in Information Office operations during the past year. Few press releases were written, but more emphasis was placed on providing detailed background on current issues to individual reporters and on writing articles for a variety of journals and other publications. Information Office staff members prepared comprehensive requests for exemption from the printing moratorium for the Age Page (1982 issues), Special Report on Aging 1982, The Baltimore Longitudinal Study of Aging, Women Over 65, and Menopause and Aging. We assisted program staff in preparing concept clearances or requests for exemption for Biological Markers of Aging, Toward an Independent Old Age: A National Plan for Research on Aging, Inventory of Longitudinal Studies of Middle and Old Age, Leading Edges, and The Macroeconomic-Demographic Model of the U.S. Retirement Income System.

Age Page

The Information Office has been very successful in obtaining outside funding for the printing, reprinting, and distribution of Age Pages. To date, the following organizations have made or are seriously considering making financial commitments for publication of Age Pages: the Digestive Diseases Clearinghouse (three Age Pages on various digestive problems); the Food and Drug Administration (reprint of drug Age Page in English and Spanish); Pfizer (arthritis Age Page); National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases (diabetes and arthritis Age Pages); National Council on Alcoholism (alcohol Age Page); and the American Speech-Language-Hearing Association (a tentative commitment for two Age Pages on speech and hearing). We are currently working with Exxon Company U.S.A. and Prudential Insurance Company of America to have Age Pages (or information from them) printed and distributed in annuitant newsletters (Exxon) and at health fairs (Prudential). Prudential is also interested in our brochure on accidental hypothermia, as are several energy companies that we have contacted. One company, Blue Cross/Blue Shield, has already agreed to reprint or excerpt from Age Pages in newsletters sent to policyholders.

Agreement With Peoples Drug Stores

Since October 1981, the Information Office has collaborated with a major drug store chain, Peoples Drug Stores, on a public service program aimed at providing the elderly and their families with important health promotion information developed by the Institute. As part of this program, entitled "Living With Aging," Peoples has designed and printed a series of brochures based entirely on NIA Age Pages. Brochure topics include high blood pressure, safe use of medicines, hypothermia/hyperthermia, dental care, and nutrition.

These booklets have been displayed in literature racks in all of Peoples' 525 stores in 14 states and the District of Columbia and are free to the public. All costs involved in printing, advertising, and distributing these materials are paid for by Peoples. The Information Office supplies the written material and provides technical advice on all aspects of the program. Other services--such as guides to community resources for the elderly--are also being offered to the public through the "Living With Aging" program. During a time of increased restrictions on the production of Government publications, this collaboration has allowed the NIA to continue disseminating health education materials to a large number of people at no cost to the Government. The campaign has brought the Institute to the attention of the public, and serves as a model for other Federal agencies interested in developing cooperative arrangements with private corporations.

White House Conference on Aging

The Information Office played a vital role in the initiation, development, and management of a number of projects for the White House Conference on Aging. Information Office staff conceived and coordinated "Tools for the Harvest," an oral history project carried out with the Smithsonian Folklife Program. Several media reports identified "Tools for the Harvest" as one of the most successful aspects of the conference.

The Information Office also suggested that other NIH Institutes be represented at the conference and proposed mounting an NIH Health-Research Fair. Information Office staff members assisted in the design and operation of the fair, selecting photographic materials, proofreading all exhibit copy, selecting handout materials, coordinating all NIH publication deliveries, adding questions related to aging to the NIH Medical Jukebox, and supervising all exhibit personnel. Volunteers from the National Retired Teachers Association/American Association of Retired Persons were successfully trained to help staff the exhibit booths. Conference participants and NIH staff alike viewed the Health-Research Fair as an important source of information on health-related research.

Additional Information Office efforts related to the White House Conference on Aging included: updating the large NIA exhibit by installing videotape equipment and adding new demographic information, developing special press packets for the Health-Research Fair and the large NIA exhibit, and screening 95 videotapes and films for the White House Conference on Aging Film Showcase.

Cost Savings

To save on costs, the Information Office now uses fourth-class postage whenever possible. If a catalogue or article asks permission to list NIA publications that fit in a business-size envelope, we instruct them to ask requestors to send us a self-addressed, stamped envelope with their order. In addition, we have arranged for some newsletters and journals which announce NIA materials to have interested readers write directly to them for copies; we then supply enough copies (in bulk) to meet anticipated needs and the publication handles the individual requests. Hospital Pharmacy Briefs and Public Health Reports are two publications that routinely announce and mail out copies of NIA booklets.

The Information Office has cooperated with a number of organizations which have reprinted and distributed NIA brochures. The National Retired Teachers Association-American Association of Retired Persons reprinted 50,000 copies of the brochure Q & A: Alzheimer's Disease. The Alzheimer's Disease and Related Disorders Association reprinted 75,000 copies of this booklet and the Canadian Societe Alzheimer plans a French edition. Finally, the Center for Accidental Hypothermia and the New York Chapter of the American Red Cross have reprinted large quantities of A Winter Hazard for the Old: Accidental Hypothermia.

In closing, we would like to report a comment made by a worker in the NIH Mail Room. He remarked that for such a small Institute, we get an awful lot of mail...in his estimation, we are surpassed only by the National Cancer and National Heart, Lung, and Blood Institutes. That's the kind of notoriety we like!

Ongoing Activities

1. Respond to inquiries from older people and their families, members of Congress, physicians and other health care providers, media representatives, scientists, students, faculty, social workers, and staff of other Federal agencies
2. Fill requests for NIA publications and refer those wanting non-NIA materials to the appropriate source
3. Maintain complex inventory of publications (stored in four different locations)
4. Provide information on NIA research interests, the grants process, and grant application procedures
5. Provide guidance to NIA staff regarding concept clearance and publication procedures
6. Coordinate NIA responses to Freedom of Information requests
7. Handle requests for speaking engagements and interviews with Dr. Butler, including: recommending whether to accept or decline; suggesting other NIA or outside speakers as appropriate; maintaining an up-to-date speech and interview calendar; and updating Dr. Butler's *curriculum vitae* as necessary
8. Represent the NIA at meetings, and speak before various (mostly local) groups
9. Maintain mailing list and press call list
10. Screen Washington Post, New York Times, Wall Street Journal, Christian Science Monitor, Time, Newsweek, U.S. News & World Report, Science, New England Journal of Medicine, Journal of the American Medical Association, and Medical World News and clip articles related to aging
11. Maintain extensive subject files of press clippings
12. Stock 5th floor hall exhibit

Announcements/Press Releases

COMPLETED

1. Press advisory on hyperthermia (spring 1981)
2. Aging Update on biomarkers conference (holding until publication of book)
3. Press release on hypothermia (disapproved)
4. Aging Update on hypothermia with cover letter announcing the availability of Special Report on Aging 1981 and Progress Report on Senile Dementia of the Alzheimer's Type
5. Press release on new Advisory Council members (in clearance)

IN PROCESS

1. Press release on heat-related illnesses

Annual and Other Reports

1. Annual Report FY81 -- wrote Office of the Director and Information Office sections; compiled and processed entire NIA submission
2. NIA section of NIH Almanac FY81
3. Scientific Directory/Bibliography FY81 -- twice yearly
4. Special Report 1982 -- for House Appropriations Committee
5. Developments in Aging 1982 -- for Senate Special Committee on Aging
6. Program Review 1981
7. NIA Freedom of Information Report FY81
8. NIA section of Diabetes Special Report 1982 -- editing, clearance, transmittal
9. NIA section of Arthritis Special Report 1982 -- editing, clearance, transmittal
10. NIA section of Genetics Special Report 1982 -- editing, clearance, transmittal
11. NIA section of NIH Publications List 1982
12. 1982 Communications Plan to HHS
13. Reports to the Office of Management and Budget on:

    --proposed reductions in periodicals, pamphlets, and audiovisual products in FY81 and 82

--inventory of planned periodicals and recurring pamphlets

--publications distribution costs in FY82

--publication reprints/revisions planned for FY83

--anticipated savings in printing of recurrent publications

Projects

COMPLETED

1. Worked with the Smithsonian Institution to produce and promote "A Seasoned Eye" calendar featuring works by older artists

2. Summarized major NIA research advances from 1960 to 1980; summarized recent research advances for Secretary Schweiker

3. Revised and updated Dr. Butler's bibliography

4. Updated NIA publications list

5. Prepared bibliographies/reading lists on:

   --organizations concerned with aging
   --information sources
   --university centers in gerontology
   --general readings on aging
   --retirement
   --sexuality and aging
   --older women
   --geriatric medicine

6. Assisted Dr. Butler in guest editing a special issue of Generations magazine on Aging and Sexuality

7. Revised NIA orientation videotape

8. Renegotiated NIA addressing and mailing contract

9. Developed guidelines for program staff in handling press contacts

10. Judged films and helped select those to be included in film series at the White House Conference on Aging

11. Worked with Smithsonian Institution to develop "Tools for the Harvest," an oral history project that interviewed White House Conference on Aging delegates and observers (results will be published by the Smithsonian)

12. Evaluated 36 scientific papers to determine suitability for condensation into lay brochures for the White House Conference on Aging, and selected 13 to summarize

13. Wrote questions for the NIH Medical Jukebox for the White House Conference on Aging

14. Coordinated NIH Health-Research Fair at the White House Conference on Aging: "Your Health From Head to Toe"

15. Designed dementia and GRC testing booths for the White House Conference on Aging Health-Research Fair

16. Refurbished and staffed NIA exhibit at the White House Conference on Aging (this included developing new demographics and videotapes to replace the slide-tape show in the original exhibit)

17. Arranged to have older volunteers assist at the NIA exhibit at the White House Conference on Aging

18. Developed policy and procedure guidelines for preparation, clearance, and printing of publications

19. Developed policy and procedure guidelines for clearance of articles and speech texts

20. Drafted policy and procedure guidelines for use of outside publishers

21. Compiled listing of NIA publications available through the Government Printing Office

22. Prepared 1981 Update to Research Training Opportunities brochure

23. Answered selected questions and edited other programs' responses to questions from the House and Senate Appropriations Committees

24. Provided public information support on pilots study, including copy-editing of final report, preparation of press backgrounder, and printing and distribution of report

25. Wrote Information Office section of NIA report to the National Advisory Council on Aging

26. Coordinated NIA suggestions for *Journal of the American Medical Association* column topics

27. Wrote radio public service announcements on accidental hypothermia

28. Critiqued brochures prepared by Project Energy Care on hypo- and hyperthermia

29. Served as consultant for Project Energy Care TV spots on hypothermia

30. Advised Hypothermia Task Force (with representation from HHS, Office of Consumer Affairs, ACTION, and AoA) on the medical accuracy of their materials

31. Reviewed chapter on accidental hypothermia for the American Physical Fitness Research Institute

32. Prepared chronology of NIA activities on hypothermia for Dr. Butler and House Select Committee on Aging

33. Reviewed House Select Committee on Aging brochure on hypothermia and prepared talking points for Dr. Butler

34. Wrote proposals to Dr. Ringler and Dr. Brandt concerning use of older volunteers for publications distribution

35. Wrote script for documentary on aging for Warner/Amex children's cable, Nickelodeon

36. Assisted program staff in the preparation of a report on nutrition information and education materials for the Nutrition Coordinating Committee

37. Prepared report on current status of national and local cable systems for Dr. Butler

38. Completed detailed questionnaire on NIA nutrition activities and publications for Directory of Organizations Involved in Nutrition

39. Reviewed article on estrogen use for McCalls magazine

40. Revised summary of NIA grant mechanisms and program announcements

41. Edited "Funding Agency Profile" for American Speech-Language-Hearing Association

42. Reviewed book-length manuscript on personal experiences of aging on Dr. Butler's behalf

43. Assisted the Epidemiology, Demography, and Biometry Program in developing and producing a slide show on its population study

44. Prepared a summary of proposed deregulation of nursing homes and continued to monitor this situation

45. Promoted Biological Mechanisms in Aging to scientific and technical journals and handled distribution to interested readers

46. Furnished analyses and reports on long-term care policy development, including regulatory and cost-control issues

47. Reviewed and edited case statement for the Alzheimer's Disease and Related Disorders Association

48. Assisted Pamela Field with preparations for a series of "Health Field" shows on aging (cancelled due to studio scheduling problems)

49. Worked with ABC's 20/20, Cable News Network, Chicago Tribune, and Washington Post on programs/articles on aging

50. Worked with PBS's NOVA on its show on aging

51. Worked with the American Association of Retired Persons on TV spots and public information materials on Alzheimer's disease

52. Reviewed Readers Digest article on mental problems

53. Reviewed speech to nongovernment organizations for Joan Bush of the United Nations

54. Provided background to Lasker Foundation on NIA senility initiative

55. Reviewed and arranged printing of NIA/National Institute of Neurological and Communicative Disorders and Stroke research initiative on senile dementia of the Alzheimer's type in the NIH Guide to Grants and Contracts

56. Assisted Neuroscience of Aging program with agenda, press calls, and other arrangements for meeting on the Neurochemistry of Senile Dementia of the Alzheimer's Type

57. Reviewed final reports of the Behavioral Sciences Research Program/ National Science Foundation contract and arranged for clearance and printing

58. Provided staff liaison between the Alzheimer's Disease and Related Disorders Association and the NIA

59. Gathered information on geriatric assessment clinics in New York, Philadelphia, Baltimore, and Washington

60. Reviewed article on senility for Current Contents

61. Edited Pennsylvania Alzheimer's Disease and Related Disorders Association chapter booklet on senility and patient care

62. Worked with People Drug Stores on "Living With Aging" campaign (included reviewing their advertising copy and editing Age Pages for republication)

63. Arranged to have Blue Cross/Blue Shield reprint or excerpt Age Pages in newsletters sent to their policyholders

64. Prepared bibliography of materials on exercise for the elderly

65. Made editorial comments and suggestions on House Select Committee on Aging report on Alzheimer's disease

IN PROCESS

1. Translation of additional--current and future--Age Pages into Spanish (will provide translations to groups of Spanish-speaking elderly; will print a limited number of copies ourselves when funds permit)

2. Updating demographic charts for lay audiences and producing demographic fact sheets on aging

3. Compilation and translation of classic cases in aging

4. System for designating historical publications

5. Further investigation of use of older volunteers for publications distribution from space in Federal Building

6. Redesign of NIA publications

7. Investigating procedures for using the National Technical Information Service for publication printing and distribution

8. Directing/editing documentary on aging with Warner/Amex for possible presentation on children's cable, Nickelodeon

9. Changing position descriptions of public information specialists to new public affairs specialist series

10. Evaluation plan proposal for information program assessment

11. Participating in plans for celebration of 25th anniversary of the Baltimore Longitudinal Study of Aging

12. Negotiating with other Federal agencies and private companies for financial support for the printing and distribution of Age Pages in their areas of interest

13. Campaign on heat-related illnesses, with special emphasis on communicating with electric companies

14. Contacting local and national cable networks to encourage interaction and joint projects

15. Assisting Senate Special Committee on Aging with preparations for farewell hearings for Dr. Butler

16. Farewell press reception for Dr. Butler

Brochures, Fact Sheets, and Books

COMPLETED

1. Lay summaries of scientific papers prepared for the White House Conference on Aging

    --Aging and the Family
    --Sex Differences and Aging
    --Aging and Digestion
    --Aging and the Circumstances of Death
    --Learning, Memory and Aging
    --Sleep and Aging

--Aging and Drugs
--Aging and Minorities
--Nursing the Aging
--Osteoporosis and Aging
--Aging and Alcohol
--Accidents and Aging (not published due to weaknesses in the original paper
--Aging and Retirement (not published due to weaknesses in the original pape

2. Special Report on Aging 1981*

3. What Is Aging Research?*

4. What Is Geriatric Medicine?*

5. Progress Report on Geriatric Medicine*

6. Progress Report on Senile Dementia of the Alzheimer's Type*

7. Fact sheets for the White House Conference on Aging on:

    --Older Women
    --Minorities
    --Poverty

8. Interim Report on the National Research Plan on Aging

9. Special Report on Aging 1982 (not yet published)

10. National Institute on Aging (complete revision; not yet published)

11. The Baltimore Longitudinal Study of Aging (not yet published)**

12. Exercise and the Elderly (not yet published)**

13. Biological Markers of Aging (not yet published)**

14. Toward an Independent Old Age: A National Plan for Research on Aging (not yet published)**

15. Inventory of Federally Supported Research in Aging (not yet published)**

16. Leading Edges**

17. Inventory of Longitudinal Studies of Middle and Old Age (assisted in preparation of concept clearance)

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* Written during FY81, but designed, laid out, and printed during FY82.

** Assistance to the programs took the form of guidance on moratorium exemption requests, other clearance and printing forms, copyediting, checking for conformance to GPO style, design, and preparation for printing.

REPRINTED
1. _Q & A: Alzheimer's Disease_

IN PROCESS
1. _Menopause and Aging_

2. _Women Over 65_

3. Revision of _Welcome to the NIA_

4. _Age Words--A Glossary of Gerontology_

5. _The Macroeconomic-Demographic Model of the U.S. Retirement Income System_**

Age Pages

COMPLETED
1. Taking Care of Your Teeth

2. Foot Care for Older People

3. Sexuality in Later Life

4. Estrogens: How Does a Woman Decide? (not yet published)

5. When a Husband or Wife Dies (disapproved)

6. Don't Take It Easy--Exercise!

REPRINTED
1. Finding Good Medical Care for Older Americans

2. Food: Staying Healthy After 65

3. High Blood Pressure: A Common But Controllable Disorder

4. Senility: Myth or Madness?

5. Safe Use of Medicines for Older People

IN PROCESS
1. Crime and the Elderly

2. Constipation

3. Arthritis

4. Diabetes

5. Alcohol Abuse

6. Osteoporosis

7. Dietary Supplements

8. Prostate Problems

9. Coping With Older Parents

Articles/Speeches

COMPLETED

1. The New Gerontology (University of Rochester Forum on Aging and the Quality of Life)

2. Research: A Hope for the Future (Revista Costarricense de Ciencias Medicas)

3. Pharmacology and Aging (Psychopharmacology Bulletin)

4. Finding Good Medical Care (Senior Citizens News)

5. Edited Foreword and Chapter 12 of Leading Edges

6. Senile Dementia: Reversible and Irreversible (Counseling Psychologist)

7. Alzheimer's Disease and Senile Dementia: The Federal Role in Research (for textbook for first-year medical students)

8. Presentation on Information Office Activities in FY81 to the National Advisory Council on Aging

9. Speech on Health Issues, Aging Research, and Older Women (Conference on Health Issues of Older Women)

10. Abstract of speech at Conference on Physical Fitness and Aging

11. Edited transcript of speech at National Cancer Institute/NIA Working Conference on Perspectives on Prevention and Treatment of Cancer in the Elderly

12. Assistance with article on Geriatrics (Journal of the American Medical Association)

13. Care of the Elderly: Special Needs for Special People (Medical Times)

14. Edited Charting the Conquest of Senility (Bulletin of The New York Academy of Medicine)

15. The Truth About Senility (Washington Post)

16. Editorial assistance on Introduction to Scientific Papers (Journal of the American Geriatrics Society)

17. Prospects and Advances in Geriatrics (Mount Sinai Journal of Medicine)

18. Nursing Research and the Teaching Nursing Home (American Journal of Nursing)

19. Letter to the Editor (U.S. News & World Report) on Van Tassel interview

20. Arts, Humanities, and Older Americans (Proceedings of NCOA Policy Symposium on the Arts, Humanities, and Older Americans)

21. Edited and articulated portions of the National Research Plan on Aging

22. The Teaching Nursing Home (Encyclopaedia Brittanica)

23. The Future: Prospects for Change (Principles of Geriatric Medicine)

24. NIA Highlights Senility Research (News & Features from the NIH)

25. Senility: The Outlook is Bright (World Health magazine)

26. The Myth of Mental Deterioration (WHO Encyclopedia de la Sante)

27. Overview of Current Research Efforts (House Select Committee on Aging Report on Alzheimer's Disease)

28. Edited Introduction to Generations Special Issue on Aging and Sexuality

29. Edited The Triumph of Age: Science, Gerontology and Ageism (Bulletin of The New York Academy of Medicine)

30. Care of the Elderly, Research, and Technology (Joint WHO/Serono Symposium)

31. Letter to the Editor (Washington Post) on Mary McGrory column on hypothermia (never published)

32. Letter to the Producer (60 Minutes) on Alzheimer's disease segment (not used on air)

33. Research on Senile Dementia of the Alzheimer's Type (Generations)

34. Safe Use of Medicines (Senior Citizens News)

35. How Summer Heat Affects You (Senior Citizens News)

36. Edited and proofread galleys of Nutrition and the Physiology of Aging (Nutrition in the 1980's: Constraints on our Knowledge)

37. Edited Introduction to Biological Markers of Aging

38. Edited Foreword to Inventory of Federally Supported Research on Aging

39. Organization and Mission of the NIA (NIA Advisory Council Handbook)

40. Dr. Milo Leavitt Heads NIA Program on Hypothermia (Undersea Medical Society newsletter Pressure)

41. Speech for Dr. Butler at the PHS National Hispanic Heritage Week meetings

42. Foreword ("A Seasoned Eye")

43. Edited Families, Institutions, MDs Share Responsibility for Care of Aging (interview with Dr. Butler in Hospital Progress)

44. Remarks on the relationship of research and services (White House Conference on Aging)

45. Article on the need for research planning for meeting of directors of gerontology institutes

46. Kober Lecture (Georgetown Medical School)

47. Article for the World Health Organization on health in old age and changing images of aging (World Health Day 1982)

48. Talking points for Travelers Insurance Symposium on Meeting an Aging Workforce

49. Revised Dr. Butler's remarks on The Century of Old Age (WHO/Japan meeting)

50. Preface (The Baltimore Longitudinal Study of Aging)

51. Edited Dr. Rapoport's Medicine for the Layman speech on the brain for possible publication

52. Edited Behavioral Sciences Research statement on monkey colonies for the NIH Guide to Grants and Contracts

53. Edited summary of Conference on Senile Dementia of the Alzheimer's Type and Related Disorders: Ethical and Legal Issues Related to Informed Consent (Journal of the American Medical Association)

54. Statement for Secretary Schweiker on NIA research on senile dementia

55. Edited Behavioral Sciences Research statement on "What Is Aging?" (Funk & Wagnall's)

56. Edited referral guideline for Neurosciences of Aging program

57. Edited Neurosciences of Aging program statement (Neurobiology of Aging newsletter)

58. Assisted in the preparation of a program announcement on pharmacology

59. Assisted in the preparation of a summary of the Second NIA Workshop on Pharmacology

60. Foreword (Victimization of the Elderly)

61. Speech for April board meeting of the Alzheimer's Disease and Related Disorders Association

IN PROCESS

1. Geriatrics (Oxford Companion to Medicine)
2. Geriatric Medicine in the United States (Textbook of Geriatric Medicine and Gerontology)
3. Senile Dementia of the Alzheimer's Type (Scientific American)
4. Article on senility (TWA Ambassador)
5. NIA Grantee Studies Sleep and Aging (Journal of the American Medical Association)
6. Testimony and scheduling of witnesses for House Select Committee on Aging hearings on senility
7. Search for Health columns on exercise, foot care, and crime

NIH Record Stories

COMPLETED

1. Adult Skin Cell Samples Yield Information on Normal Aging Patterns
2. NIA, Smithsonian Produce Older Artist Calendar
3. Peoples Drug Stores to Distribute Free NIA Aging Brochures to the Elderly
4. NIA to Participate in Sessions, Exhibit at Third White House Conference on Aging
5. Alleged "Anti-Aging" Drug Needs More Basic Research (DHEA)
6. NIA Grantee Continues Research at Age 90
7. The Hispanic Elderly
8. Hypothermia
9. Aging Does Not Impair the Heart Muscle
10. Tamoxifen Treatment Benefits Rabbits with Osteoarthritis
11. Merit Awards for Ann Dieffenbach and Suzie Porter (photo and caption)
12. NIA Hosts Meeting of Directors of Gerontology Institutes (photo and caption)
13. Swedish University Honors Dr. Butler
14. NOVA Features Aging Research
15. Recent Stride Graduate David Mineo Receives Financial Award
16. Biomarkers Could Be Clues for Intervening in Aging Process

IN PROCESS

1. NIA and Warner-Amex Produce Cable TV Documentary on Aging

2. Interview with Dr. Butler

3. Intelligence Can Improve with Age

4. Dr. Vijaya Melnick Appointed to Nestle Infant Formula Audit Commission

Conferences Covered

1. Biological Markers of Physiological Aging (NIA)

2. Neurochemistry of Senile Dementia of the Alzheimer's Type (NIA)

3. Building Partnerships: Older Americans and Their Energy Suppliers (sponsored by the White House Office of Consumer Affairs)

4. Convocation on Nutrition Education for Older Americans (sponsored by ITT Continental Baking Company and the American Dietetic Association)

5. Fitness and Aging (sponsored by the President's Council on Physical Fitness and Sports and General Foods Corporation)

6. National Medical Association annual meeting (took exhibit)

7. White House Conference on Aging (exhibited, directed NIH Health-Research Fair, cosponsored oral history project with Smithsonian)

8. National Advisory Council on Aging meetings

9. National Hispanic Heritage Week

10. World Health Organization meeting on information transfer

11. Board meeting of the Alzheimer's Disease and Related Disorders Association

12. Annual meeting of the American Federation for Aging Research

13. Working Conference on Perspectives on Prevention and Treatment of Cancer in the Elderly (National Cancer Institute/NIA)

Report of Behavioral Sciences Research Program

Scope of the Program BSR-1
Program Goals BSR-1
Program Structure BSR-2
Current Program Activities BSR-4
Equal Employment Opportunities BSR-6
Evidence of Program Performance BSR-6
Scientific Accomplishments BSR-7

BEHAVIORAL SCIENCES RESEARCH

Scope of the Program

In contrast to the narrower focus of most other National Institutes of Health, the National Institute on Aging (NIA) is mandated to deal with the person as a whole. NIA's mandate is to conduct and support "biomedical, social, and behavioral research and training related to the aging process and the diseases and other special problems and needs of the aged." As one of the two extramural research programs of NIA, the Behavioral Sciences Research program (BSR) is concerned with the psychological, cultural, social, and economic factors that affect the process of growing old, the place of older people in society, and the maintenance of health and effective functioning in the middle and later years.

This mandate defines a large and complex area that draws upon many behavioral science disciplines and requires convergence with the biomedical sciences as well. The need for new knowledge throughout this area derives not only from the exponential increases in the length of a person's life and in the proliferation of older people in the population; the need derives also from the growing awareness that social and psychological factors are strategically important in influencing the aging process, in maintaining health and well-being, and in preventing disease. This is a particularly challenging time for research in the BSR program: it is a time when the Surgeon General reports that over half of U.S. deaths are attributable to behavior and life style; a time when increasing scientific attention is given to the interplay among social conditions and the changes with aging in the brain and in the interrelated endocrine, immunological, and other physiological systems; a time when the unprecedented extension of longevity means that human competence endures far beyond the average age of retirement; a time when technological changes in the workplace are transforming occupational opportunities for people of all ages; a time when the disabilities, dependencies, and institutionalization of the very old must be forestalled before they become overwhelming.

Program Goals

To provide the knowledge base for dealing with the special problems and needs of the aged, the small Behavioral Sciences Research program has addressed this large and compelling task. In the two and a half years since its reorganization, it has evolved two overarching objectives within which special goals and initiatives are formulated:

1. To understand the aging processes, as biological aging interacts with psychological aging and with the social environment.

   Here the concern is to define and explain the age-related changes in the major behavioral systems (sensori-motor, intellectual and cognitive, emotional and motivational); the adaptative capacities of these systems; and the modifiability of physical, mental, and social functioning in relation to varying social conditions.

2. To understand the place of older people in the changing society and in various institutional arrangements (such as families, communities, health care facilities, economic and political organizations).

Here the concern is to specify the ways in which changing societal and cultural conditions and social networks affect people in their middle and later years in respect to mortality, the burden of illness, socioeconomic status, needs and attitudes, and the opportunity to lead productive lives.

These broad goals provide a blueprint for long-range planning. They give coherence and direction to the diverse research activities in many disciplines and institutions here and in other countries. And they serve to raise the level of excellence of BSR's contributions to the complex mosaic of accumulating knowledge in this large area.

Based on BSR's early experience with these two broad goals, a third, more sharply focused goal has been defined and given immediate attention during FY 1982:

3. To specify the particular social, psychological, and behavioral mechanisms and conditions enhancing health and effective functioning in the middle and later years.

   Here the emphasis is on four types of age-related processes linking behavior to physiological, psychological, and social functioning:

   a) Direct psychophysiological effects of stressful conditions (e.g., work pressures, family disturbances, geographical mobility) on neural, endocrine, immunological, and other physiological responses known to change with aging.

   b) Social support and coping as mediators of stress.

   c) Health habits and lifestyles (e.g., smoking, diet, exercise, etc.) as these vary with social conditions.

   d) Reactions to illness as these may promote health or influence pathogenesis, by the patient (e.g., resistance to immunization, minimization of symptoms, compliance with treatment) and by medical caretakers (e.g., negative stereotypes of old people, confusion of pathology with aging, inadequate attention to older patients).

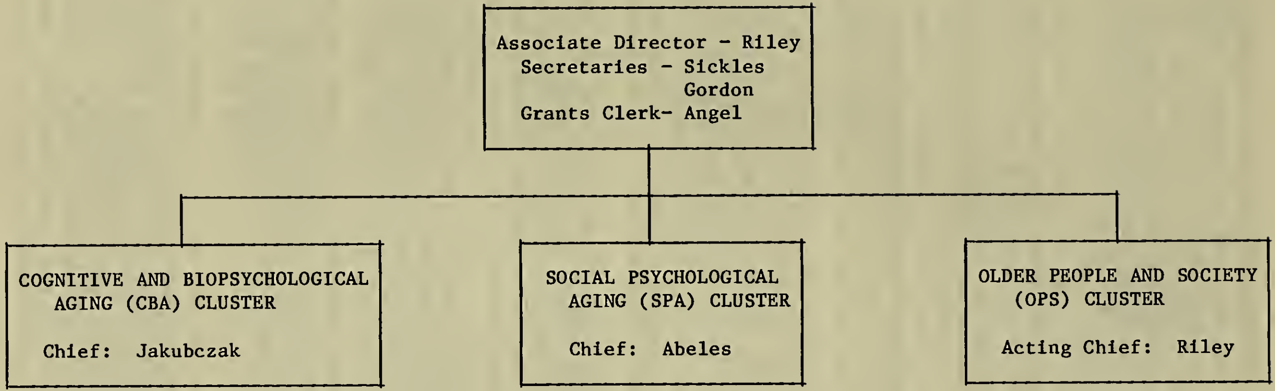
Thus, within the broad framework of goals 1 and 2, BSR's current efforts are directed toward providing the knowledge base for prevention and postponement of disability and dependence, and for probing the linkages between the changing social environment and such potentially preventable or reversible disabilities as chronic ill health, sensory deficits, memory loss, low self-esteem, or exclusion from active participation in the labor force.

Program Structure

Coordinate with these goals, BSR has organized its structure and functions and deployed its personnel as indicated in Chart A. BSR is now divided into three major clusters of program areas, as follows:

CHART A

BEHAVIORAL SCIENCES RESEARCH PROGRAM
STRUCTURE AND ORGANIZATION



Associate Director - Riley
Secretaries - Sickles
Gordon
Grants Clerk- Angel

COGNITIVE AND BIOPSYCHOLOGICAL AGING (CBA) CLUSTER

Chief: Jakubczak

SOCIAL PSYCHOLOGICAL AGING (SPA) CLUSTER

Chief: Abeles

OLDER PEOPLE AND SOCIETY (OPS) CLUSTER

Acting Chief: Riley

Areas

a) Cognitive Aging (CA)
Jakubczak
b) Biopsychological Aging (BA)
Jakubczak (acting)

Areas

a) Psychosocial Aging (PA)
Abeles
b) Biosocial Aging & Health (BAH)
Ory

Areas

a) Age in the Population (AP)
Ory (acting)*
b) Age and Societal Structures (ASS)
Bond (acting)*
c) Older People and Social Institutions (OPI)
Bond

Support Staff: Danzik

---

*HSA being recruited

I. COGNITIVE AND BIOPSYCHOLOGICAL AGING (CBA)--concerned with the identification and specification of cognitive, intellectual, and perceptual changes and stabilities that, interacting with biological processes, occur with aging.

a) Cognitive Aging--supports research and training on constancy and change in the processes of sensation, perception, attention, memory, learning, cognition and intelligence, motivation, creativity, wisdom, and psychomotor performance.

b) Biopsychological Aging--supports research and training on the relationships between behavioral aging on the one hand, and neurological, immunological, and endocrine aging, on the other. It includes studies in neuropsychological assessment, behavioral genetics, and nutrition.

II. SOCIAL PSYCHOLOGICAL AGING (SPA)--concerned with the changes and stabilities with aging in the health, behavior, personality, and attitudes of people as related to the social environment.

a) Psychosocial Aging--supports research and training on changes and stabilities with aging in the effective functioning, productivity, attitudes, personality, and interpersonal relationships of individuals as related to the social environment. It includes cohort and longitudinal studies on the relationship between aging and such topics as stress and coping, social supports, personality traits and processes, social perception and emotion, attitudes, self-image, life satisfaction, life-course transitions and interpersonal relationships.

b) Biosocial Aging and Health--supports research and training on how social and environmental processes, interacting with biological processes, influence health and functioning in the middle and later years. It includes socioenvironmental intervention experiments for preventing or reversing age-related decrements in physical health. It also includes longitudinal studies of the interrelationships among health, attitudes, and behaviors; sociobehavioral mechanisms for health promotion and disease prevention; interplay among work, health and aging; social, environmental and technological factors associated with age-related changes in the need for and utilization of long term care.

III. OLDER PEOPLE AND SOCIETY (OPS)--concerned with the changing societal and cultural conditions, and the groups and social institutions, that affect people in their middle and later years with respect to mortality, the burden of illness, socioeconomic status, needs and attitudes, intergenerational relationships, and the opportunity to lead productive lives.

a) Age in the Population--supports research and training on the changing social and demographic structure of society as a whole. It includes a wide range of demographic and epidemiological research on such topics as: morbidity, mortality, causes of death; patterns of migration, rural-urban residence; age composition of the population; distribution of the older population by sex, race, ethnicity, social class, etc; and the implications of these population distributions for health and illness, family structure, education, income maintenance, and the like.

b) Age and Societal Structures--supports research and training on the influence of societal structures on behaviors, attitudes, health, and statuses of older people. It includes studies of the roles of older people; the relation of age to laws and to differential opportunities for productivity, income, work, education, and political participation; age-based conflict and age-integration vs. age-segregation; cross-cultural and cross-temporal variabilities; and the influence of sex, race and ethnicity, and social class on older people's roles.

c) Older People and Social Institutions--supports research and training on how, and with what consequences, people are influenced by the intricate network of social institutions in which they grow old: families, households, communities, work organizations, educational and religious institutions, political institutions, health care and welfare institutions.

During FY 1982, BSR staff has actively encouraged applications in these three program clusters, which address the two major BSR goals of understanding both the aging processes and the place of older people in the changing society. Cross-cutting the entire program, the efforts of staff and Associate Director have been directed toward sharpening the focus on the third goal of promoting health and effective functioning.

Current Program Activities

In pursuit of its goals, BSR as currently restructured is engaged in a range of activities required to develop and manage grants and contracts and to meet related programmatic objectives. Active grants and contracts for FY 1982 numbered less than 200 and were funded at approximately 15 million dollars, as in Table 1.

1. Grants. In order to stimulate relevant research applications from top-flight investigators, two general program announcements have been issued sequentially: "Social and Behavioral Research on Aging, 1979" (reissued in FY 1982) and "Health and Effective Functioning in the Middle and Later Years, September, 1981". These announcements are to be followed by more highly focused announcements, as on "Work Roles, Productivity, and Health" or on "Functioning of Frail Elderly in the Household." The general announcements have also served to place within the conceptual framework of the new program three previously issued (1978) announcements: "Retirement and Aging", "Aging and Bereavement", and "Minority Aging".

Ongoing research grants address BSR goals on a variety of topics, such as: sensory and perceptual processes; memory and reasoning, psychosocial components of senile dementia, hypertension, menopause, sleep, exercise, nutrition; flexibility in attitudes, personality; stress, coping, and social supports; work and retirement; bereavement; health maintenance; mortality, morbidity; age composition of the population; older women; ethnicity; family and household, etc.

Table 1

Behavioral Sciences Research

ACTIVE AND PROJECTED FOR FY 1982

Unofficial estimates as of 7/8/82

CLUSTER	TRAINING F32, F33, T32, K04		RESEARCH P01, P50 R01, R03, R13 R21, R23			CONTRACTS & INTERAGENCY AGREEMENTS		TOTALS	
	No.	Amount		No.	Amount	No.	Amount	No.	Amount
a) Cognitive & Biopsychological Aging (CBA)	14	$ 823,738	R01	39	$ 3,170,858	2	$ 104,814		
			P01	5	$ 1,309,099				
			Other	14	$ 645,820			74	$ 6,054,329
b) Social Psychological Aging (SPA)	1	$ 16,380	R01	31	$ 3,890,780	3	$ 122,500		
			P01	0	-0-				
			Other	7	$ 257,669			42	$ 4,287,329
c) Older People in Society (OPS)	10	$ 580,618	R01	38	$ 3,658,906	0	$ -0-		
			P01	1	$ 204,640				
			Other	4	$ 166,482			53	$ 4,610,646
TOTALS	25	$1,420,736		139	$13,304,254	5	$ 227,314	169	$14,952,304

Findings are beginning to suggest how the productive middle years might be extended; how many disabilities of old age might be prevented or postponed; and how the costs of health care and dependency might be contained.

2. Other programmatic objectives. Apart from activities devoted to development of applications and management of grants, staff is working toward the following specific objectives essential for achievement of program goals in this developing area of research:

- Recruitment of scientific manpower to the study of aging;
- Conceptual clarification of aging as a dynamic, multifaceted process; and of the associated changes in psychological, social, and physical functioning;
- Development and application of methods for precise measurement of age-related changes in functioning; and for dynamic analysis of longitudinal and cohort data;
- Substantive integration and evaluation of scientific knowledge, so that NIA applications may be appropriately assessed and the findings may become cumulative;
- Coordination with the far-flung related programs of other public and private agencies in the United States and abroad;
- Development of research resources (human study populations, animal colonies, computerized data archives);
- Dissemination of scientific knowledge to the scientific, lay, professional, and policy-making communities.

BSR staff has engaged in a variety of activities directed toward these programmatic objectives, including:

- In respect to Health Promotion/Disease Prevention, providing staff support to the Deputy Director/NIA and the NACA Working Group in this area.
- Organization of major workshops and conferences and publication of associated papers on "Work, Aging, and Health" and on "Age and Anthropological Theory" and (with other National Institutes of Health) on "Women: A Developmental Perspective" and on "Prevention and Treatment of Cancer in the Elderly;" and (with the private sector) on "Population Aging: Consequences for Social Institutions and Human Service Organizations."
- Organization of symposia at numerous scientific and professional meetings, dealing with varied aspects of health, behavior, and aging, and resulting in publication of several papers.
- Active participation in two major Committees of the Institute of Medicine (IOM): the Committees on Health and Behavior, and the Committee on Stress.

- Leadership of the NIH/ADAMHA Steering Committee for the IOM Project: "Health and Behavior: A Research Agenda;" initiation and leadership of the NIH Working Group on Health and Behavior.

- Convening of a series of NIA Behavioral Sciences Research Seminars, and a second series of NIH Seminars on Health and Behavior.

- Participation in several interdisciplinary and international conferences on such topics as psychosocial factors in prevention and treatment of cancer in the elderly, developmental views of older women, cross-cultural perspectives on retirement.

- Support of two centrally important research committees as extensions of NIA staff: the Committee on Life-Course Perspectives in the Middle and Later Years (Social Science Research Council) and the Committee on Aging (National Academy of Science).

- Establishment of procedures for allocating budgetary and personnel resources to support program implementation.

Equal Employment Opportunities

BSR has worked closely with the Special Assistant for EEO to the NIA Director in furthering the goals of equal employment opportunity within BSR, NIA, and the scientific community. Efforts have been made to identify minority scientists and to encourage their participation in BSR sponsored activities, including research and training. A number of grants by or about minorities have been funded. Communication has been maintained with minority institutions throughout the country and with the minority fellows sponsored by the American Psychological Association and the American Sociological Association. Continuing efforts are made to identify minority professional and support personnel for the few positions that have been available at BSR. BSR is closely informed on EEO policies, plans, and programs; takes care to see that these are disseminated to all staff members; and is committed to the principles of merit promotion, fair treatment, appropriate recognition, career development and full utilization of skills of all employees, irrespective of race, religion, color, sex, national origin, age, or handicap.

Evidence of Program Performance

Although no neat and easily applicable criteria have ever been developed for evaluating the scientific enterprise, all possible indicators are utilized in subjecting the BSR program to a continual process of critical scrutiny and evaluation. As judged by the available indicators, the program has made significant contributions to the knowledge base; raised the quality of research proposals; attracted many promising younger scholars and several distinguished scientists to the field of aging research and teaching; contributed to both theoretical and methodological development; disseminated new knowledge through four specially commissioned volumes, many scientific articles, and professional speeches; added to extant research resources (data archives, longitudinal study populations, non-human primate colonies); and served as an effective liaison to NIH, ADAMHA, National Academy of Sciences Committtees on Vision and Hearing, Institute of Medicine, the Social Science Research Council Committee on the Life Course, the American Association for the Advancement of Science, the

International Gerontological Society, the World Health Organization, and many other organizations and agencies.

Scientific Accomplishments

While revolutionary discoveries or theoretical breakthroughs rarely occur in a single year, scientific knowledge is beginning to take shape in the BSR program and knowledge gaps needing new research continue to be identified. The program is contributing to the already existing massive scientific support for three fundamental, though little recognized, principles:

- That aging is a psychosocial as well as a biological process. Research shows that the way people age is affected by their life styles, educational levels, nutrition, self-care, economic status, social expectations, family relationships, and many other social and psychological factors. The recognition of the importance of the brain to the endocrine, immune, and other physiological systems - themselves changing with age - leads to new research questions on how accumulating behaviors and social stresses feed through the brain and the mind to affect these systems.

- That aging is not fixed for all time, but changes as society changes. Research shows that growing old in 1981 is very different from growing old in 1881 or in 2081; and growing old in contemporary Appalachia is very different from growing old in Grosse Pointe, Michigan. Since people do not grow old in laboratories the recognition that people at different times and in different places age in different ways leads to new research questions on how particular social and historical conditions influence aging.

- Because aging is not immutable, it is subject to a degree of human intervention and control. Research shows that modifications in attitudes, behaviors, social relationships and environments can often prevent, postpone, or reverse disabilities currently associated with old age. The recognition of the mutability of the aging process leads to new research questions on how appropriate interventions can optimize this process.

CBA. Striking evidence of the mutability of aging is being adduced throughout BSR as illustrated in the Cognitive and Biopsychological Aging cluster. Many age differences, earlier regarded as inevitable decrements due to aging, are found to disappear or even reverse when appropriate controls are introduced for such explanatory factors as educational level, health status, habits of diet and exercise or other aspects of life style. Moreover, intervention studies are demonstrating how age-related deficits in memory, reaction time, and intellectual (as well as in physiological and in social) functioning can often be reversed under appropriate conditions of retraining, performance incentives, or learning of new strategies. The accumulating body of knowledge is shedding fresh light on the conditions and mechanisms for sustaining high levels of cognitive functioning into the later years.

Building on this knowledge, several lines of research on Cognitive Aging need development. The highly specialized findings on specific aspects of cognition need to be integrated into a systemic model of information processing.

Many laboratory findings need testing for their relevance to real-life situations. Cross-section studies of age differences need to be complemented by longitudinal studies that examine aging as a process. And performance tests, many of them originally designed for subjects at one particular age, need modification to become applicable across the life course. Meantime, the new area of Biopsychological Aging is barely beginning to explore the crucial linkages among genetic disposition, age-changes in behavior, and the neurological, immunological, and endocrine components of the aging process.

SPA. Projects in Social Psychological Aging, by focusing directly on aging as a dynamic process, are uncovering some important findings. Early childhood experiences, once thought to fix the template of personality and attitudes for the remaining life course, can no longer be seen as indelible. Over the middle and later years of life, patterns of aging, and the consequences of such life crises as bereavement or retirement, vary widely depending upon such mechanisms as coping, self-image, or social support. Social and environmental conditions influencing the aging process are being specified through longitudinal analyses of work roles or through experimental interventions in the treatment of elderly patients in nursing homes.

New lines of development here require building on the great strengths of this program cluster: on the continuing use of computerized data archives and human study populations; on the developing methodologies for longitudinal and cohort analysis; and on the "natural experiments" that can identify propitious opportunities for intervention in the aging process.

OPS. The program cluster on Older People and Society is sharpening the methodology of calculating life expectancy at the older ages, as the dramatic and unpredicted extensions of life resulting from changing life styles and medical advances are having profound consequences both for the aging process and the proliferation of older people in society. Unprecedented issues are arising that require entirely new understandings of the societal factors associated with the differing degrees of health and morbidity in the older population. Research is identifying the emerging social conditions and relationships affecting the problems, needs, status and well-being of older people. And as four, even five, generations of a family survive, and the age of widowhood is postponed, new analyses are being made of such social institutions as the family and health care institutions which influence and are influenced by older people.

Continuing Implementation of the Focus on Health and Effective Functioning

As the BSR program progresses, selected aspects of health and effective functioning are being defined for special attention. Important new ground is to be broken if the goal of maintaining health, productivity, independence, well-being and effective functioning of older people is to be met. The special challenge is less to outside investigators, few of whom are yet aware of the remarkable potential in the BSR program; instead, the major challenge is to BSR staff who must specify the key issues and must formulate the researchable propositions. The mandate, but not the details for implementing it, is set forth in the 1982 National Research Plan on Aging. As implementation, staff has selected several topics for priority attention and is proceeding to develop bibliographies and state of the art papers, to assess existing findings and identify gaps needing research, and to communicate with networks of potentially interested scientists.

The program announcement on Health and Effective Functioning in the Middle and Later Years, issued in September, 1981, has alerted the scientific community to the central focus of BSR's concerns and has already stimulated over 2,000 inquiries. However, in order to guide the formulation of significant and researchable objectives, to challenge outstanding scientists, and to insure the excellence of proposals, further developmental activities along several selected lines are necessary. A cost-effective strategy is being used, which involves primarily small workshops leading to program announcements, small groups of research advisors, seminars, journal publications, and other inexpensive means of communication with potential grant applicants. Several workshops and task groups are already underway and others are scheduled for the future. They address eight key components of the focus on Health and Effective Functioning in the Middle and Later Years.

Changing Work and Aging Workers

This is the first of two Task Groups on Social Contexts of Effective Functioning in Middle and Later Life, designed to specify the social conditions that maintain or enhance functioning and productivity as people grow older. Already underway in FY 1982, this group serves as a model for those to come. A small continuing core group of consultants, representing academic, corporate, and government sectors, and supplemented by ad hoc consultants as needed, has met several times in FY 1982. The objective is to examine and clarify the nature of the interplay between changing work roles and aging workers. A variety of activities are involved, including the preparation of bibliographies and working papers by BSR staff with the advice of the Task Group. Of the two workshops planned for FY 1982, both focus on technological changes in work and their impact upon work roles, aging, and human performance. The first (May 1982) emphasized gender differences, and the second (September 1982) emphasized social class differences in these complex interactive processes. Another component of the changing work role, the introduction of "wellness programs," is also under scrutiny. Continuing meetings are planned for FY 1983 with the goal of specifying particularly promising research topics within the overall domain of the Task Group. These activities will result in journal publications and the issuance of sequential program announcements. A special feature of this Task Group is its close collaboration with the private sector (most immediately with the Equitable in New York), in line with the successful experience of NHLBI in working with industry to reduce hypertension, thereby enhancing productivity and reducing absenteeism.

Independent Living in the Household

This second Task Group on Social Contexts of Effective Functioning is designed to complement the focus on the workplace in specifying the conditions that can sustain the health, well-being, and independence of the very old and that can reverse or offset disabilities when they occur. Scheduled for September 1982, a small planning meeting will address the cost savings to society and to old people themselves of keeping the growing numbers of frail elderly out of nursing homes. New research is needed to add to the growing body of knowldege as to how particular health behaviors and attitudes of older people are influenced by particular features of their living conditions—ranging from the attitudes of relatives, neighbors, and health care practitioners to the availability of improved prostheses, special environmental designs, wellness clinics, and other community supports. The topic is related directly to the emphasis on Health and Effective Functioning and to the program on Teaching Nursing Homes.

These two continuing Task Groups will lead to a series of program announcements; they will stimulate a range of researches into the psychosocial, biological, and health outcomes of particular social contexts; and they will point to the potential for interventions to modify such contexts.

Cognitive Processes over the Life Course

This is the first of a series of small workshops designed to encourage conceptualization and operationalization of components of intellectual functioning that are valid and reliable, not only in childhood like most standard measures of "intelligence," but over the full life course. This first workshop, which is jointly funded by the Max Planck Institute (Berlin), and for which Dr. Paul Baltes has agreed to serve as co-chairman, will concentrate on concepts potentially crucial for later life development, such as creativity, wisdom, and experience-based decision making. Filling an important gap in BSR's program of maintaining and enhancing functioning in the middle and later years, this first workshop and its published proceedings should lead to the first of a series of program announcements, should provide the nucleus for an BSR advisory work group in this area, and should lay the groundwork for subsequent workshops.

Research on Methods of Longitudinal and Cohort Analysis

Also designed as a series are small workshops to encourage development and application of increasingly powerful methods of dynamic analysis of the aging process. These workshops are essential to BSR's central concern with longitudinal methodology, and to the application of this methodology to the new emphasis on health and effective functioning in the middle and later years.

In particular, this new emphasis requires methods for interrelating over the life course sequences of behaviors (e.g., stopping smoking, taking up exercise regimens), life events (e.g., moving, losing a job or a spouse), and physiological changes (e.g., in lipid levels, blood pressure). In addition to longitudinal studies of aging in a single cohort (of persons born at the same time), methods of cohort analysis are needed for comparing members of different cohorts. For example, in an important BSR project, Featherman and Sorensen are beginning to attack the problem of how the timing and sequencing of life events are influenced by industrialization, urbanization, and other changes in societal institutions and populations.

In this series of workshops, the first, to be chaired by Drs. Featherman and Sorensen, will deal with methods of analysing the influence of changes in a single society on variabilities in the aging process. Later workshops will address the influence on aging of cross-cultural and cross-national differences, as well as a range of other analytical problems.

In addition to journal publication and continuing communication to the scientific community, BSR plans to issue (and periodically update) methodological guidelines for grant applications involving longitudinal and cohort analysis. Thus the series of workshops, and a work group of advisors selected from the participants, will serve to improve the quality of research applications received by NIA/BSR through encouraging methodological advances and the more appropriate use of existing methodology.

Research on Mnemonics, Memory Loss, and Aging

Designed to investigate the use of mnemonics to minimize memory loss among older people, this workshop will consider means of remediation of memory loss among older adults; identify gaps within the science base and between the science base and the clinic; and recommend strategies to narrow these gaps. Ultimately for the benefit of working scientists, the workshop will contribute to an important area of BSR's emphasis on maintaining Health and Effective Functioning in the Middle and Later Years. It will also contribute to BRCM's initiatives in geriatric medicine and in teaching nursing homes. On the basis of the workshop, a BSR program announcement will be developed.

Design and Development of Data Bases in Behavioral Sciences Research

As a resource for NIA biomedical and behavioral researchers, the need for NIA's support of preexisting longitudinal samples of human respondents will be assessed. This resource would be parallel to the NIA-supported colonies of nonhuman animals. Several important longitudinal samples are currently in danger of ceasing data collection because their samples have aged and are thereby no longer essential to the needs of the sponsoring agencies. However, the very aging of such samples makes certain studies relevant to NIA. In some instances, the infusion of relatively small amounts of money may result in the continuation of data collection, or the extension to include additional psychosocial or health-related variables. Thus, the potential exists for the creation of a major resource through NIA's support of these samples and the eventual archiving of the resulting data. The Task Group will be charged with three tasks:

1. Establish criteria for selecting for NIA support ongoing or recently terminated longitudinal studies which have the potential for increasing knowledge of the aging process (e.g., full age range, national representative samples, minority samples, special samples of old people, length of previous longitudinal records).

2. Review studies as candidates for NIA support and make recommendations for how such candidates could be made maximally relevant to NIA's concerns (e.g., adding particular variables).

3. Establish criteria for setting up new longitudinal studies, as they may be essential to supplement existing populations.

Aging Nonhuman Primate Set-aside Colonies

BSR intends to establish--with the cooperation of BRCM and OPEA--a Task Group to provide NIA with recommendations for the use and management of the NIA/DRR Aging Monkey set-aside colonies as an animal research resource for biomedical and behavioral scientists. A panel of experts will develop and recommend guidelines for the utilization and administration of the set-aside colonies.

Reduction of Risk Factors

An integrated series of activities is planned for developing the macro-social components of BSR's Health and Effective Functioning in the Middle and Later Years initiative, with a particular emphasis upon health. BSR's current program already has considerable strength in terms of supporting research on effective functioning at the individual level of analysis. The program is already attracting researchers interested in social and behavioral factors in health, but mainly (again) at the individual level of analysis. For example, BSR is supporting research on health and individual coping styles, stress, and social support from small groups. Such studies tend to ignore the more social structural or macro-, supra-individual processes. However, studies are needed at the macro-level to examine the spread through the population of health related behaviors and the conditions of the effectiveness of these behaviors. Consequently, BSR intends to encourage such research, to recruit an HSA with expertise in this area, and to initiate a series of activities as the first step towards this goal.

Barriers to Program Performance: Administrative Issues

A start has been made. Yet a significant gap exists between those responsibilities and the research program so far underway. The program is recently reorganized; some critical initiatives have only recently been activated; and some major emphases are still underdeveloped.

A number of barriers have been identified which inhibit the optimum development of the BSR program. At this juncture, most lacking are:

- Scientific manpower with the requisite skills for conducting interdisciplinary research. The problem is partly one of training. Post-doctoral training programs are needed in those few institutions equipped to train at the interdisciplinary leading edge. Post-doctoral fellowships and program projects (including Teaching Nursing Homes) are being featured as means for bringing together psychosocial and biomedical scientists. Moreover, the introduction of a special Interdisciplinary Research Award is being considered. The development of interdisciplinary talent requires more than mechanisms and funds for training and research. The entire scientific community, including NIH review panels, must be apprised of the importance of relating health and behavior within the aging perspective.

- Conceptual models which specify the mechanisms and conditions that influence health and effective functioning and the processes of psychosocial aging in general. Means for critically reviewing and codifying existing knowledge and for encouraging conceptual development are required. For example, an updating of Aging and Society: An Inventory of Research Findings would be a major step in this direction.

- Further development and wider application of research methods. Many measures of human performance, designed for use with the very young, require revision for use across the lifespan. Methods are needed for analyzing continuous life histories; for linking social change to the aging of individuals; and for causal analyses of interrelated medical, behavioral, biological, and social variables. Researchers need to become expert in the use and interpretation of existing and emerging analytic methods.

- Expansion of research resources to permit use by investigators of existing human study populations and data archives. Longitudinal and cohort research is expensive, both in terms of money and time. Consequently, ongoing projects need to be made maximally useful to a wide range of researchers and existing data should be made available for secondary analyses. BSR is supporting the continuation of worthy study populations through small, but symbolically important contributions. For the future, potentially worthy study populations need to be identified and criteria for selecting among them need to be developed. Moreover, data archives--such as the University of Michigan's--need to be encouraged and supported.

- Coordination among diverse programs and agencies. In order to magnify the impact of its relatively small resources, BSR makes contributions to projects supported mainly by other federal and private agencies. For example, BSR contributes to the support of two National Academy of Sciences committees and plans to supplement the funding of a third committee. Longer-range plans call for continuing development of working relationships (for conferences, seminars, identification of research sites, use of available records and study populations, etc.) that can stimulate innovative applications in a range of organizations. These plans constitute extensions of activities already initiated, such as: the collaborative conferences with NCI, NICHD, and NIMH; the working relationships with such private organizations as the American Council of Life Insurance or The Equitable; the cooperative funding with the Max Planck Institute or the Academy for Behavioral Medicine Research; the NIA leadership in conferences on health and behavior with NIH, ADAMHA, and the Institute of Medicine. These examples are merely suggestive of the potential extensions of the scientific influence of the small BSR program. However, difficulties in negotiating sole source contracts interfere with links to such strategic networks as the National Academy of Sciences and the Social Science Research Council. Moreover, restricted travel funds curtail working relationships with more distant agencies.

- Sufficient personnel for full implementation of BSR's program. With a handful of people, a vast amount of work is accomplished. However, the strain on these few is heavy. At least, two additional clerical and administrative staff are needed. In addition to the medical sociologist currently being recruited, a biopsychologist is urgently required in order to develop the critical biopsychological component of CBA.

  The amount of skilled and careful staff work required to develop a single fundable grant (one that is both scientifically sound and relevant to the NIA program) cannot be over emphasized. In 1982 BSR funded 169 projects. All these projects require continued monitoring of progress reports and evaluation of contributions to scientific knowledge. But these fundable projects represent only a small fraction (less than one-fourth) of the applications that come in for review (represented by the pink sheets). These pressures on staff are especially acute because BSR is at an early stage of development, established in its present organizational mode less that 3 years ago, and because the BSR program constitutes a new scientific area concerned with the interrelations among health, behavior, and aging. The staff is very small. Yet the mandate is very broad--covering at least 9 separate scientific disciplines.

- Adequate office space. Short-handed as BSR is now, the professional and secretarial staff are crowded together, HSAs must double up, and there is no place either for file cabinets or for visitors. As soon as the needed additional staff is recruited, the shortage of office space will again become intolerable.

- Travel funds for program development. Development of a program, and maintenance of high standards of excellence, demand interaction with professional societies, research centers, foundations and business organizations, and other agencies pursuing directions of common concern. BSR invariably schedules travel on the most cost-effective basis, where sizeable numbers of scientists can be seen at one place, can be informed of NIA's programs, and can discuss developments and problems in their own institutions. Thus, great efforts are made to be cost-effective in utilizing BSR's limited travel funds. However, the existing travel budget is inadequate to such a degree that BSR staff often pay for their travel with personal funds.

Considerable effort is underway to overcome these barriers. Through its work with related national and international programs in behavioral medicine, biopsychology, and medical sociology, BSR is contributing to the development of new and relevant paradigms for understanding health and behavior. The BSR program has planned a variety of activities (workshops, commissioned papers, symposia, state of the art assessments, program announcements) to stimulate the required conceptual, methodological, and substantive advances and the recruitment of cross-disciplinary scientists to conduct research on aging, health, and behavior. Given adequate backing, BSR stands ready to develop the necessary psychosocial component of NIA's mandate.

Report of Biomedical Research and Clinical Medicine Program

Program Description BRCM-1
Program Highlights BRCM-1

BIOMEDICAL RESEARCH AND CLINICAL MEDICINE PROGRAM

PROGRAM DESCRIPTION

The Biomedical Research and Clinical Medicine Program (BRCM) supports research and research training for geriatric medicine, physiology of aging, and the molecular cellular basis of aging processes. The Program was reorganized in 1981. It is now comprised of the Geriatrics Branch, the Physiology of Aging Branch, and the Molecular and Cell Biology Branch. The personnel associated with each branch and section are presented in Figure 1. The major objective of this organization is to encourage research on the basic aging processes and their impact on major organ systems and to facilitate the transfer of that knowledge to studies of geriatric problems.

The Office of Resource Development is responsible for administration of the aging animal colony and the cell line repository as well as the development of new models to support research and aging.

PROGRAM HIGHLIGHTS

The Animal Resources Program, supported through the contract mechanism, has for several years provided standardized colonies of Sprague-Dawley and Fischer 344 rats. Because of decreased demand by investigators, the contract supporting the Sprague-Dawley strain was terminated in January 1981. The Fischer 344 will be continued since it is considered to be the best rat model currently available for aging research.

Five inbred mouse strains, three hybrid mouse stocks, three congenic mouse strains and one outbred mouse stock are also maintained by NIA. The BALB/c, C57BL/6, and the CB6F1 hybrid are in greatest demand.

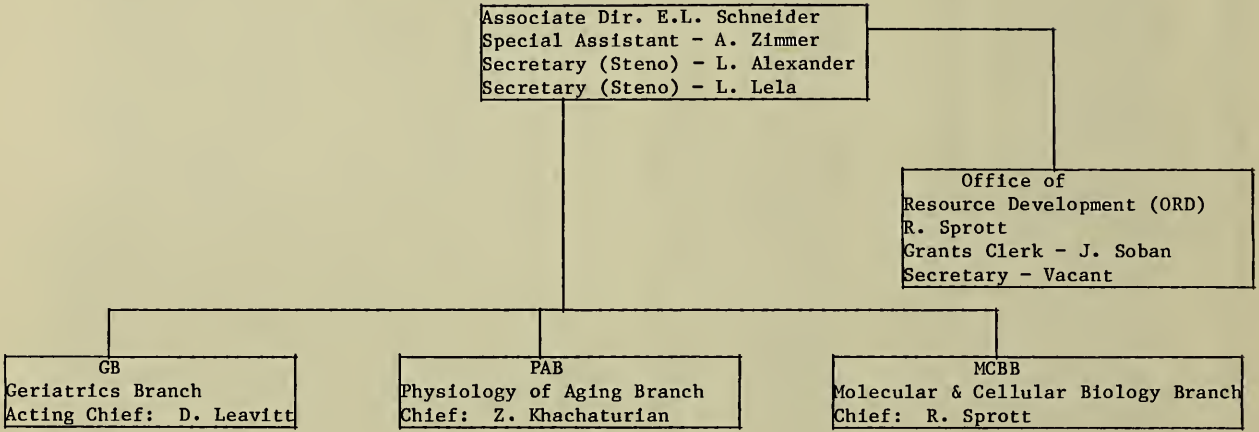
The Geriatrics Branch

It has been estimated that by the end of this century over 25 million American will have attained the age of 65, many of whom will have multiple and complex illnesses requiring significantly more medical care per individual than will younger persons.

In accord with the Research on Aging Act of 1974 (P.L. 93-296), the Geriatrics Branch, BRCM, was established not only to support biomedical research related to the aging process, but to conduct training and other activities which are necessary to fulfill that portion of the NIA mission which addresses "the diseases and other special problems and needs of the aged." Major program elements within the Geriatrics Branch include the Pharmacology Section, the Geriatric Research Section, the Dermatology Section and the Geriatric Training Section.

The major thrust of the Geriatrics Branch in collaboration with BSR involved the solicitation of Teaching Nursing Home grants. The concept of bringing the talents of the academic research community to the problems of chronic diseases and disorders of the elderly was conceived by the Director, NIA. An Announcement was issued calling for Letters of Intent to be followed by grant applications. The announcement called for the development of a teaching nursing home which would include the efforts of one or more nursing homes, a medical school, and nursing school or nursing division and one or more acute care hospitals. The grant includes support for the core activities of the teaching nursing home plus several research projects which would utilize this core. Response to the Announcement by Letter of Intent and 18 grant applications.

BRCM
Organization



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PAB
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MOLECULAR BIOLOGY R. Sprott
GENETICS R. Sprott

Additional Personnel

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Grants Clerk(P/T) - K. Sacks

Pharmacology Section

The Pharmacology Section is supporting research on the incidence of adverse drug reactions and aging. It has been estimated that in the over 80 group, the incidence of adverse reactions may often be three times greater than that in the general population. Further, the use of multiple drug regimens leads to the greater probability of adverse drug-drug interactions in this population, which is probably exacerbated by the increased sensitivity of the elderly to untoward drug reactions.

It is well established that the elderly have increased responsiveness to the central effects of the benzodiazapines. The cause for this increase is under active study and recent reports suggest that the mechanism may be complex and subtle. Findings indicate that the increased risk of adverse drug reactions in the elderly to amitriptyline is not primarily due to age-related differences in drug distribution and hence must result from a change in pharmacodynamics with increasing age. With increasing age, postmaturity decreases have been observed in glutathione levels, microsomal mixed function monooxygenase activities and glutathione metabolising enzymes. It has been suggested that these changes may contribute to a decreased rate of metabolism and increased susceptibility to drugs, foreign chemicals and disease processes which occur with advanced age.

Dermatology Section

The Dermatology Section seeks to:

- establish normal values for dermatologic parameters in the elderly to facilitate evaluation of pathologic conditions;
- improve epidemiologic data on prevalence, incidence, risk factors, and complications of decubitus ulcers;
- increase understanding of cellular, tissue, and systemic changes which increase susceptibility to decubitus ulcers and impair wound healing;
- improve methods of preventing or curing decubitus ulcers and of accelerating wound healing in the elderly.

The bulk of activity in the dermatology program to this point has concentrated on descriptive studies of age-related changes in skin and connective tissue. These studies have demonstrated a diminished and delayed response to skin irritants in the elderly. This observation may have important implications for the diagnosis of inflammatory disease in old age. The biochemical and cellular basis of wound healing in the aged rat is being explored and a minimally invasive system has been developed to examine the phenomenon in humans.

Geriatrics Research Section

The Geriatrics Research Section is supporting studies of disorders which are concentrated predominantly among older people (e.g., osteoporosis, benign prostatic hypertrophy, urinary incontinence) or which are associated with increased morbidity and mortality in the elderly (e.g., fall injuries, pneumonia). The medical management of these problems is complicated by underlying physiologic changes with age and the frequent presence of multiple disorders, often necessitating altered therapeutic strategies.

Program objectives are to:

- improve epidemiologic data on prevalence, incidence, associated risk factors, and complication of the major sources of morbidity among the elderly, particularly dementia, incontinence, hypo- and hyperthermia, pneumonia, osteoporosis, osteoarthritis, and fall injuries.

- determine normal age-related changes in those physiologic function involved in the development or prevention of major causes of morbidity and mortality in the elderly. Determination of normal values for these functions in the elderly is essential for the evaluation of etiologic or predisposing factors for disorders of old age. Factors regulating cognition, memory, temperature regulation, sleep, micturition, resistance to infection, and bone metabolism are of particular importance.

- improve understanding of the etiology and pathophysiology of the above disorders.

- evaluate effectiveness of present and new techniques for the diagnosis, prevention, treatment or cure of these disorders.

A large project to obtain a wide range of clinical pathologic data from autopsy and surgical specimens has been initiated. These studies will be valuable in establishing data on normal and pathologic changes with age in man. Another project to study changes with age in mechanical and ultrasonic properties of human bone has recently begun, and should yield important data in regard to osteoporosis and risk of fracture. Studies on impairments with age in response to cold exposure are in progress.

An epidemiologic study of international differences in mortality rates is adding to knowledge of genetic and environmental risk factors in major disease. Two epidemiologic studies are examining the role or physical activity, endocrine, and dietary factors in the development and prevention of osteoporosis, and elucidating further details on the relationship of osteoporosis to other risk factors for fractures. Clinical studies on age that may contribute to the increased incidence of hypothermia in the elderly. Studies using an animal model of osteoarthritis have increased knowledge of cartilaginous changes with age that predipose to this condition. Clinical studies to elucidate neural and vascular problems associated with impotence in elderly men are in progress. Studies on defects in extraneural tissue associated with Alzheimer's disease should clarify pathophysiology of this order and facilitate antemortem studies.

Geriatric Training Section

The Geriatric Training Section has developed the following program objectives:

- develop improved curricula in geriatric medicine and dentistry;

- increase research training opportunities in geriatric medicine and dentistry;

- develop faculty for the teaching of geriatric medicine and dentisty;

- facilitate interchange of educational ideas and methods among researchers.

Curriculum development has been a major focus of the 24 awardees of the Geriatric Medicine Academic Award. Assessment measures undertaken by several awardees shows that despite limited preexisting clinical geriatric curricula, there was strong positive student interest in geriatric medicine.

Instructional activities increased significantly. Material on geriatrics was integrated into established courses and new electives were developed. Preclinical and clinical topics included were: physiology of aging, human growth, maturation and senescence, pharmacokinetics and pharmacodynamics of aging, urinary incontinence, and externships in geriatric medicine.

Geriatric research activity by students and faculty was encouraged and developed by the awardees. One principal investigator has designed a new assessment instrument for a prospective study of nursing home patients and changes in their social and physical conditions. A student fellow initiated a research proposal which will establish norms for protein-caloric intake in an elderly population. Research on endocrine factors which affect sexuality in aging males is being continued by a principal investigator and another faculty member.

Participation in mandatory rotation in geriatric medicine for medical interns and residents, resource material development, annual conferences, establishment of fellowships and journal clubs were among other significant activities of the awardees.

The Geriatric Dentistry Academic Award program inaugurated last year is at an earlier phase of development than the medicine program. However, curriculum and research activities by the six awardees are developing in a parallel manner.

Molecular and Cell Biology Branch

The basic aging processes which underlie age related changes are the focus of this Branch. Molecular processes at the cell and tissue level must be understood if we are to achieve success in altering the course of, or preventing age related disease and "normal" age deterioration. Successful intervention and health maintenance strategies will depend on new knowledge in cell biology, genetics and molecular biology. Current emphasis in the Branch is on increased coordination of Branch programs and increased concentration on mammalian systems.

Cellular Biology:

The Cellular Biology section supports research on mechanisms of cellular aging with the use of cell culture technologies. Cellular events may significantly contribute to longevity and senescence. The study of cells as they "age" in culture and of cells derived from humans and experimental animals of various ages permits investigation of cellular events consequent to aging independent of the complexity of the whole organism. Such studies to date have mostly used fibroblast-like cells of dermal and lung origin, these being easily obtained and cultured.

The capacity to study human cells, especially cells with differentiated characteristics, independent of the parent organism has been emerging over the past decades through the technologies of cell cultured. Research on isolated cells in culture has provided remarkable access to basic knowledge of cell structure and function. Cells in culture are usually closely identified genotypically with the organism from which they are derived. However, the circumstances of the cell culture environment inevitably cause these cells to be remote phenotypically from cells *in vivo*. With proper appreciation of the limits of cell culture systems, they do provide models for comparative studies in cellular aging. The advantages of cultured cells as models for cellular aging research include 1) access to experimentation on human cells, 2) the ready accessibility of tissue to generate cultures from surgical procedures such as circumcision, skin biopsies, blood samples and autopsy, 3) the ability to study cells individually or in mass quantities, 4) the relative simplicity of, and the capacity to control the cell culture environment as compared to the *in vivo* environment, and 5) the large, highly competitive community of scientists conducting basic cell biology research on cell culture systems to understand phenomena of cell structure and function.

The Cell Biology Section encourages descriptive studies to ascertain expressions of senescence in cultured cells, and the subsequent studies to determine the mechanisms responsible for the phenomena of senescence. Somatic cell genetics, which has contributed to knowledge of chromosomal location and function of specific human genes, is a field encouraged to investigate the genetic control over cellular senescence.

The transplantation of cells and tissues, including serial transplantation progressively from one animal to the next, enables observation of senescence and survival features of cells that are genetically and/or morphologically distinct from those of the host. Similarly, chimeric and genetic mosaic animals offer the means to compare, within the organism, differential expressions of cell senescence and cell survival. Chimeric animals enable observation of development and senescence of cells of different genetic heritage within the normal tissue arrangement of one animal. This is made possible through emerging technologies enabling the incorporation of genetically distinct cells into the host organism during very early embryological stages.

In support of research in cell biology of aging, NIA maintains through a contract a cell-line repository at the Institute for Medical Research, (IMR), Camden, New Jersey. This repository acquires, develops, characterizes, stores and supplies cultures for gerontological research. The repository contains about 650 cell-lines which include human diploid fetal lung fibroblasts (IMR-90/91), skin fibroblasts from individuals of different ages and fibroblasts from individuals exhibiting features of premature aging, such as progeria and Werner's syndrome. In addition, the repository also maintains several epithelial cell lines cells from primates with different life spans.

The Cell Biology section will continue to support basic research to understand the mechanisms of cellular aging as well as theoretical biology studies which bear upon cellular metabolic age related processes. We are continually evaluating, in consultation with the scientific community, types of studies and various experimental systems best-suited for cellular aging research. Currently, normal human fibroblast-like cells are extensively used in cellular aging research. This system requires further characterization with respect to cell heterogeneity in mass culture, in vivo precursors of in vitro cultures, etc. Through a program announcement (NIH Guide for Grants and Contracts 9 (2), 1980) we are encouraging investigators to study various aspects of cellular biology of aging, using differentiated cells in culture. Such studies could provide valuable information on age-associated functional decline of various tissues and organs.

One of the cell culture systems widely used in research on cell biology of aging is the normal diploid human fibroblast-like cells (HDF) of lung and dermal origin. These cells are easily obtained and maintained in culture.

The results of a series of experiments designed to determine why some, but not all, transformed cells can induce DNA synthesis in senescent human diploid cells would appear to show that the ability to induce DNA synthesis is not correlated with transformation to either immortality, anchorage independence, tumorigenicity, or the ability to proliferate in low serum containing medium, but rather, appears to be associated with transformation by DNA tumor viruses.

In studies comparing serum deprived "G_0" and senescent cells, a number of morphologic and functional similarities have been observed. Total glycosaminoglycan synthesis decreases dramatically when both senescent and young actively growing, human diploid cells are placed in media with 0.1% serum and then increases some 10 fold in both old and young culture when 10% fetal calf serum is restored to the culture. The quiescent "G" phase of the cell cycle can be induced in young cells by serum deprivation, mitomycin or amino analogs, when these quiescent cells are fused to untreated young cells they behave similar to senescent cells with regard to DNA synthesis.

In studies on nucleo-cytoplasmic control of replication it was shown that when SV-40 transformed nuclei were fused to Phase III, WI-38 cells, the finite life span state was dominant, (AG01212, 1981). The parent with the lower proliferative potential was dominant in hybrid studies of short-lived and long-lived phenotypes. Investigation of the effect of life span of the human diploid parent on the life span distribution of hybrids resulting from fusion of diploid cells with SV-40 transformed human fibroblasts (normal X immortal fusions) showed the limited life span phenotype to be dominant. These results lead to the conclusion that cellular senescence is the result of specific genetic control processes; that immortal cells could result from malfunctioning of these processes; and that immortality appears to be a recessive trait.

Previous work had demonstrated that fibronectins isolated from early and late passage human fibroblasts were functionally distinct, (AG00697, 1980). Studies since have further characterized the functional differences and have obtained evidence supporting a structural difference in the two fibronectins. It was found that old fibronectin was defective in its capability to promote the formation of focal adhesions in either young or old cells. Using an enzyme-linked immuno absorbant assay technic, results suggest that the two fibronectins differ from each other in collagen affinity.

A new model system for study of cell aging _in vivo_ and _in vitro_ has been developed. Fibroblasts, for example, incorporated into 3-dimensional matrices, under conditions which favor cell survival, remain viable for long periods of time. The matrix, which gels when cast, consists of collagen in the presence of serum, proteoglycans and tissue culture medium. This matrix plus cells is called a "tissue equivalent" since it undergoes contraction and resembles tissue in feel and in look, but only when cells are present. The cells present in the contracted matrix remain separate from each other as confirmed by optical sectioning of contracted matrices whose cells have been stained with fluorescence diacetate or neutral red; and by electron microscopy. Using a decreased volume of the tissue equivalent as a test of cell function, it was shown that AG 1519 foreskin fibroblasts of high PDL can contract matrices at least as efficiently as cells of low PDL of the same strain.

Of interest is an understanding of the mechanism for cessation of proliferation due to terminal differentiation. Studies in pursuit of that goal have involved the development of ways to control the proliferation and differentiation of human epidermal keratinocytes (HK cells). It was shown that when HK are cultured in serum-free medium with $3\text{-}10^{-5}$M calcium, that they do not differentiate. If these proliferative cells are frozen, they show high viability on replating. Raising the calcium concentration to 10^{-3}M or adding serum to the serum-free medium causes the HK cells to become differentiated. If the calcium concentration is increased in steps, the HK cells also become differentiated in steps. It was found that if the differentiated cell populations are washed with low calcium serum-free medium, the stratified cell layers come off, leaving a basal layer of proliferating cells attached to the substratum. These developments now make it possible to obtain relatively pure populations of HK, to store these cells for use in a series of experiments, to cause the cells to differentiate at will, and to separate the presumptive differentiated cells from the proliferating cells.

A study on osteoporosis detected elevated levels of -carboxyglutamate in 8 of 10 patients with generalized osteoporosis and preliminary evidence that levels of circulating osteocalcin are also increased. These data, together with the biochemical characterization of osteocalcin, a bone protein that binds calcium, suggest that changes in the vitamin K mediated -carboxylation of osteocalcin may play a role in osteoporosis.

In a study on aging and monoamine receptors in the brain biochemical evidence was presented for selective decreases in biogenic amine receptor systems with age in the rabbit. A fifty percent decline in dopamine-stimulated adenylate cyclase activity in striatum, hypothalamus, frontal cortex and anterior limbic cortex of five-year-old rabbits as compared to one-year-old rabbits was seen. Evidence for decrease in number of dopamine receptors rather than in binding affinity was presented. Research supported to date by the Geriatrics Section has encouraged use of the fruitfly *Drospohila*, the laboratory nematode *Caenorhabiditis elegans*, the slime mold, *Dictyostelium*, the colonial flagelate *Volvox*, and the protozoa.

Fundamental knowledge of the events which control senescence in lower organisms will often provide important information for aging processes in general and human aging in particular. For this reason both genetic and comparative aging studies are encouraged by the Genetics Program in a wide range of organisms. Special emphasis is now given to mammalian genetics research since mammalian organisms are less remote from man than lower organisms and mammalian systems often offer direct evidence relevant to human genetic influences.

The first of several possible genetics colonies of experimental animals recommended in *Our Future Selves* was established by the NIA in September 1979. This resource, the Caenorhabditis Genetics Center(CGC) supports the biological community at large through services as mutant acquisition, storage, characterization and distribution. The CGC is in its third year of operation, and is recognized, in addition to be a mutant source, the national focal point for nomenclature, the genetic map and world literature reference file.

Studies of genetic factors in human longevity most frequently use twin study or cross cultural methods. In an interesting set of experiments using both techniques, Dr. Dorit Carmelli, SRI International, Menlo Park, California is studying genetic control of human longevity and pathology and developing new techniques for analysing these extremely complex problems. Analysis of the longevity of 2,424 pairs of twins and their non-twin siblings in the Mormon Geneology revealed that twins have similar longevities, that non-twin sibling's life span similarities are significant but lower than twin similarities, and that twins exhibit a life span disadvantage compared to non-twin siblings. Cross-cultural studies show different major gene effects for Angina Pectoris and Non-Fatal Myocardial Infarcts, and a major familial association between serum lipid levels and chronic heart disease. Different familial characteristics lead to early mycardial infarct rather than to angina pectoris in several culturally separate groups. These experiments suggest that powerful new analytic techniques, useful for separation of genetic and environmental longevity and disease influences, are producing valuable new insights.

Species differences in life span provide undeniable evidence of genetic programming. However, the question of whether senescence *per se* is programmed or is the consequence of genetic control of other aspects of organism function is an area of intense research interest. Using several strains of *Drosophila Melanogaster* in a variety of environmental situations it has been shown that *Drosophila Melanogaster* life span is controlled by minor genes with non-additive action and that growth rate and life span are aspects of the same phenomenon. There is an optimal food (yeast) level at which life span and growth rate are maximal, above and below this level life span is reduced; life span is positively correlated with growth rate in the low half of the range and negatively correlated with growth rate in the high part of the range.

Cytoplasmic theories of aging take two forms: Aging is due to the progressive loss of some essential factor from the cytoplasm of the cells in a clone, or aging is the result of the progressive accumulation of some deleterious factor in the cytoplasm of the cells in a clone. Using the ciliate protozoan Paramecium Tetraurelia as a clonal model system, Dr. Karl J. Aufderheid is testing both forms of cytoplasmic theory. Using micro-injection techniques to exchange young and old cytoplasm between Paramecia. This study has found the cytoplasm to be uninvolved in aging of clones. These results are in sharp contrast to results obtained in in vitro tissue culture studies of human fibroblasts. The differences observed in cytoplasmic function between invertebrates and vertebrates indicate the importance of verification of invertebrate results in vertebrate model systems. Verification of such results and resolution of differences with other model systems should contribute to our understanding of cytoplasmic vs. nuclear genetic contributions to aging processes.

The interaction between exposure to stress, development of pathology, and longevity is highly complex. Using an insect model system, studies to investigate the effects of early exposure to stress on later stress resistance and longevity are being conducted. Initial findings suggested that early exposure to X-irradiation stress retarded age-associated decline. More recent results show that the longevity promoting effect of early stress is due to increased resistance to the deleterious effects of later stress rather than an alteration in aging processes. These studies are now investigating specific biochemical effects of early stress and comparing results in insects with those obtained in mammalian systems in order to understand the mechanisms of gene-environment interaction.

A variety of studies suggest that different cell types within organisms age and senesce at different rates. Studies of genetic factors in cell death are aimed at understanding these differences. Studies of Drosophila Melanogaster have shown that many mutations in Drosophila cause cell death in very specific cell groups. Current studies are now pursuing evidence that at least some cell-death mutants represent blocks in catabolic functions so that certain cellular components accumulate and kill the cell. These studies have significance for normal aging processes and may be especially significant for the study of certain human storage diseases as well.

Taken as a whole these reports demonstrate important advances in the identification of specific genetic contributions to longevity and age specific pathology in lower organisms and suggest that some similar effects occur in higher organisms and humans. However, few of these studies show direct relevance to mammalian systems and diseases. Future development in this program will emphasize the maintenance of the program's major strength in basic mechanism research while at the same time seeking an increase in mammalian research to bridge the gap between lower organism phenomena and human genetic mechanisms. A similar shift in emphasis in the Office of Resource Development is occurring so that appropriate mammalian models will be available to support mammalian genetic research in this program.

Physiology of Aging Branch

The mission of the Physiology of Aging Branch (PAB) is to foster the development of scientific knowledge and to facilitate the translation of basic medical and scientific information into practical application for the treatment and care of elderly patients. The PAB has responsibility for five programs: Neuroscience, Immunology, Nutrition, Exercise/Physiology and Endocrinology. Since these programs have a complementary scientific interrelationship, they are integrated into a single Branch of the Biomedical Research and Clinical Medicine Program (BRCM) of the National Institute on Aging (NIA). The primary thrust of the PAB programs is to encourage the development of integrated clinical and basic research in the biomedical sciences represented within the Branch. The PAB, as a unit within BRCM, through its component programs fosters research on age-related physiological processes at the tissue organ, organ system and organismal levels.

Neuroscience:

The Neuroscience of Aging Program (NAP) supports research on the relationship between aging and the nervous system (NS). The program fosters a spectrum of research within neuroscience whenever the focal point of investigation is the aging process and concomitant changes in the structure and function of the NS. The program axiomatically regards the aging NS as an entity which has distinctly altered physiological attributes; consequently, the aging NS is a subject worthy of investigation as a separate area of neuroscience. The specific aim of the program is to encourage the development and dissemination of information in both basic and clinical neuroscience.

Alzheimer's Disease (AD), also known as senile dementia of the Alzheimer's type (SDAT), afflicts 5 percent of people over the age of sixty-five; its diagnosis depends on the presence of two characteristic brain lesions, referred to as tangles and senile plaques, observable only in postmortem brain tissue. Although plaques and tangles occur in small though increasing numbers in normal aging, they accumulate excessively in Alzheimer's disease. Excessive numbers of plaques and tangles are also observed in about 75 percent of Down's Syndrome victims who may begin to show signs of premature senility in their twenties and thirities. In normal nerve cells, thin strands of protein (neurofilaments) are woven smoothly throughout the cell body, but in these two lesions the protein strands have become twisted together in pairs called paired helical filaments (PHF). Gathering in clumps, they deform and probably kill the nerve cell. Until recently neuropathologists believed that the proteins which form the characteristic neurofibrillary tangles and senile plaques in AD were proteins like any other. Dr. Dennis J. Selkoe a neuropathologist at McLean Hospital, investigated whether in fact the proteins in the lesions behave as other proteins behave. He has found that the proteins of the Alzheimer's lesions are highly insoluble. Through a series of experiments he has demonstrated that the PHF in Alheimer's lesions contain a highly rigid large polymer whose molecules are held together by an extremely strong bond - a covalent cross-link. This type of cross-linking of structural protein, i.e. covalently bound insoluble polymers, exists in human erythrocytes, skin keratinocytes and senile cataracts. Dr. Selkoe's data provide evidence, for the first time, that such high molecular weight covalently cross-linked proteins can occur in nerve cells. More recently Dr. Selkoe has demonstrated that transglutaminase is present in the human brain and can cross-link normal human neurofilament proteins into an insoluble high molecular weight filamentous polymer. On the basis of these data, Dr. Selkoe has proposed a testable model (hypothesis) for age related fibrillary degeneration of human neurons. It is very likely that the gradual accumulation of permanent, highly rigid fibrous polymers may irreversibly alter the functioning of nerve cells. Dr. Selkoe's findings are extremely important and exciting because now we can begin to investigate the exact nature of the cross-linking bond and the causes. In doing so, scientists may find a point at which they will be able to intervene in the disease process of AD and prevent or slow its development.

At present, little is known about the etiological factors that influence the rate of brain aging. Dr. Philip W. Landfield, Bowman Gray School of Medicine, is testing the hypothesis that endocrine factors, particularly glucocorticoids may normally accelerate some aspects of brain aging. In an earlier study Dr. Landfield had reported that long-term adrenalectomy does reduce some morphological correlates of aging in the rat hippocampus which is rich in corticosterone receptors. In a more recent study Dr. Landfield has demonstrated that long-term treatment of rats with a neural stimulant, pentylenetrazole (PTZ), or with a potent and behaviorally active analog of the ACTH (4-9) molecule, which does not affect glucocorticoid release, can retard the development of both neuromorphological and behavioral correlates of brain aging in rats. Dr. Landfield's data indicate the possibility that certain endogenous peptides with stimulant properties may exert trophic long-term effects on brain structure and function.

The scrapie agent, after infection and a prolonged incubation period, causes a degenerative disorder of the central nervous system in sheep and goats. The transmission of kuru to chimpanzees by Gajdusek and his associates in 1965 has led to a major rethinking about the etiology of all degenerative disorders and made scrapie a subject of intense research interest. One of the major unanswered questions in molecular biology concerns the chemical structure of the scrapie agent. Dr. Stanley B. Prusiner, University of California-San Francisco, has made considerable progress in explaining the macromolecular structure of the scrapie agent. He has shown by several separate and distinct lines of evidence that the scrapie agents require a protein for infectivity. Although the scrapie agent is irreversibly inactivated by alkali, five procedures with more specificity for modifying nucleic acids have failed to cause inactivation. Because the novel properties of the scrapie agent distinguish it from viruses, plasmids and viroids, Dr. Prusiner has proposed a new term "PRION" to indicate a small PROteinaceous INfectious particle which is resistant to inactivation by most procedures that modify nucleic acids. Dr. Prusiner's finding is very exciting because it may provide a significant lead for understanding the causes of several degenerative diseases such as AD.

Nutrition:

The Nutrition Program of PAB supports research in the areas of diet and nutrition (both basic and clinical) as these relate to the aging process and the problems and needs of the aged individual. Areas of more basic research include the role of nutrition in the aging process itself and in the pathogenesis of diseases common among the elderly. More applied areas of research include nutrient status assessment and nutrient requirements in both healthy elderly and those with chronic diseases or on chronic drug regimens. Physiologic changes which are commonly found in the elderly and which affect or are affected by nutrient status also represent research areas relevant to the goals of this program. Examples include age-related changes in gastro- intestinal function and in taste and smell, as well as those changes in immune and endocrine function which are related to nutritional factors. Since many of the problems and diseases of the elderly have their origins in earlier adult life, research into the effect of nutrition during the earlier adult years on the diseases and problems of the elderly is also of interest.

Adequate nutrition is key to the promotion and maintenance of health during all stages of the life cycle. In the elderly, adequate nutrition may mean the difference between an active, productive individual and one who is physically and emotionally disabled the thus in need of more frequent medical attention, less resilient in the face of such stresses as accidents, disease and surgery, and more likely to require hospitalization and even institutionalization. In addition, diet is one factor over which the individual can exercise a major degree of control during large portions of the life cycle. Thus, nutrition research is an area of great importance to the NIA and one which urgently needs expansion.

The assessment of nutritional status in elderly populations is plagued by questions concerning the level to which, for any given nutrient, the term 'adequate' should be applied. A level which differs from that considered adequate for a younger individual may be just as inadequate for the elderly person as it would be for the younger one, or it may represent a change in the set point for that nutrient. That is, it may represent part of the normal aging process and be relatively unresponsive to alterations in nutrient intake. These issues are being addressed by NIA grantees at the University of Arkansas (Dr. Carol O. Mitchell) and at the University of New Mexico in Albuquerque (Dr. James S. Goodwin). Dr. Goodwin is carrying out a 5-year prospective study of the effects of subclinical malnutrition on the physical health and life expectancy of 270 community dwelling elderly people. This subject population can be described as healthy, on no medications, and of relatively high socioeconomic status. The nutritional status of each individual is evaluated yearly by clinical exams, a three day diet record with weighed intake, and a battery of biochemical analyses of a sample of blood. These individuals are also being evaluated immunologically with skin tests, and *in vitro* mitogen responses in an effort to determine whether the depressed immune function often found in the elderly correlates with subclinical malnutrition.

The study is in its third year and some interesting findings are beginning to emerge. Analysis of the dietary intake data indicates that energy, vitamin and mineral intakes from diet alone were adequate with the possible exceptions of calcium and vitamin D intakes in the women. Energy intakes (expressed as percent of the recommended dietary allowance - RDA) were 90% for men and 87% for women, while for protein, only 11% of the men and 14% of the women failed to get at least 100% of the RDA. In this population 16% of the men and 20% of the women were classified as obese on the basis of a body weight of more than 120% of their 'desirable' body weight. Approximately 60% of both men and women took one or more vitamin and/or mineral supplement with vitamins C and E the most popular. Biochemical analyses on the blood samples obtained during the first year of the study are being examined in relation to dietary intake. The mean plasma ascorbic acid level for the women was significantly higher than that for the men (1.30 mg/dl vs 1.13 mg/dl). Less than 2% of the population were at risk for developing clinical symptoms of vitamin C deficiency. However, it was estimated that maintenance of a plasma ascorbic acid level of 1.0 mg/dl would require an intake of 75 mg/day for women and 150 mg/day for men. This suggests a need for a revised RDA for vitamin C (the current value is 60 mg/day for both men and women) with a separate and higher value for men than for women. Approximately 45% of the population were taking some supplemental riboflavin. A significant correlation was found between total riboflavin intake and riboflavin status as measured by erythrocyte glutathione reductase activity. However, inadequate riboflavin status did not appear to be a problem in this population. On the other hand, vitamin D status (assessed by plasma concentration of 25-hydroxyvitamin D) does appear to be a problem. Plasma vitamin D was significantly lower in these elderly than in a younger control population. Within the elderly population, plasma vitamin D showed a seasonal variation with the peak in September and the trough in January. Levels were consistently higher for men than for women. In addition, plasma alkaline phosphatase, an index for bone loss, was inversely related to plasma vitamin D concentration. Inadequate dietary vitamin D intake and inadequate sunlight exposure both appeared to contribute to the low vitamin D status. The finding of low vitamin D status in this population is especially noteworthy since it would appear to be a favored group both in terms of income and educational levels adequate for obtaining good nutrition and in terms of residence in a sunny climate.

Exercise:

The objective of the Exercise Physiology Program Section is to promote and support basic and clinical research of age-associated biologic changes that are induced by acute and chronic (training) physical activity. The experimental approaches range from the sub-cellular to the organismic level. The applicability of this research to the elderly in American society is of crucial concern. Research issues of special importance include the extent to which the elderly can physiologically respond and adapt to single and repeated bouts of moderate and moderately-severe physical activity and the underlying and predisposing determinants for this. The development of physical activity programs which can be individually prescribed to optimize physical fitness in the elderly is one of the principal aims of this program section.

Physical exercise may forestall and/or ameliorate many of the functional impairments of the elderly. Exercise in early or mid-life may modify the age-related changes that normally occur in various physiologic systems so that the incidence and/or severity of disease of the elderly is significantly reduced. Furthermore, exercise in later life may help the elderly to overcome already existing age-related conditions. However, the scientific evidence concerning the most effective kinds of exercise for the various age strata or the mechanism by which exercise can exert its influence is meager. Moreover, little or no evidence has been collected concerning the effects of exercise in the elderly on physiological systems (e.g., endocrine, nervous, and immune systems) which interact with the cardiovascular, pulmonary, renal, and musculoskeletal systems. Thus, the main focus of the Exercise Physiology Program (EPP) is to encourage and support research whose aim it is to assess the impact of exercise in early, middle as well as late life on the function of the cardiovascular, pulmonary, musculoskeletal and renal systems in the elderly. This focus encompasses an interest in fostering research which delineates the normal age-related changes that occur in these systems as well as the mechanisms and pathways by which various forms of exercise exert their effects on these systems. To the extent that the mechanisms have an endocrine, neurological, immune, or nutritional component, the EPP will complement research supported by other programs in the Physiology of Aging Branch.

During FY 1981, projects supported by EPP covered research in cardiovascular capacity, musculoskeletal and motor functioning, renal and liver functioning and responses to special environmental conditions in the elderly. Among the highlights of this research is a project conducted by Dr. David B. Dill of the Las Vegas Desert Biology Research Center, (R01 AG00437). Dr. Dill, who was honored by the National Advisory Council on Aging at the January meeting for his continued interests in the response of the elderly to extreme environmental conditions, has been studying the response of the elderly from various ethnic groups to exercise in extreme heat. Among other things Dr. Dill has found that there are no major differences in thermoregulation during three one-hour walks in desert heat at rates of walking ranging from 60 to 120 meters per minute. Major differences were noted between males and females, with women having a lower sweat rate and higher skin temperature than men.

Dr. John Holloszy (R01 AG00425) of Washington University has been investigating the effects of exercise on several factors in aged Long Evans rats. He has found that, in skeletal and heart muscle, exercise forestalls the age-related decline in the activity of glycolytic enzymes, the mitochondrial enzymes and in the capacity to oxidize fatty acids or pyruvate. It also appears that, while there is a modest decline in skeletal muscle weight with age, the capacity of muscle to adapt to exercise with an increase in respiratory capacity is retained.

Another major initiative in the project by Dr. Holloszy concerns the effects of exercise on glucose tolerance, glucose transport and oxidation by fat cells. He reported that the moderate deterioration in glucose tolerance with age could be prevented by requiring animals to swim two hours per day. Twenty six month- old swimmers had blood glucose levels lower than that of the sedentary group even though the swimmers had lower plasma insulin levels. There were no differences in blood glucose or insulin response between the 9 and 26 month old swimmers indicating that the swimming exercise could reduce the age-related changes in these two measures.

Dr. Evertt Smith of the University of Wisconsin (R01 AG01029) has been investigating the effects of exercise in 35 to 65 year-old women on bone loss and cardiovascular functioning. The exercise program involves activities such as swimming, treadmill walking, cycling, and jogging. Subjects are required to perform at 70-85% of maximum aerobic capacity three times per week for 50 minutes. After one year on the exercise program results of treadmill stress tests revealed significant declines in heart rate, systolic and diastolic blood pressure, and a significant increase in oxygen utilization. Measurements of bone loss are preliminary but appear to support the conclusion that exercise reduces the rate of normal age-related calcium depletion. These latter results are also consistent with preliminary findings reported by Dr. Stanton Cohn of Brookhaven Memorial Laboratory (R01 AG00919).

Many published studies have shown that there is a progressive age-related loss of muscle mass. One possible factor associated with this phenomenon is the tendency toward reduced activity with increasing age. Dr. Frank Streter at Boston Biomedical Research Institute (R01 AG02103) has hypothesized that the reduced activity could, in turn, reduce the neural and biochemical stimulation of muscle fibers thus resulting in their overall decline. Working at the molecular level, Dr. Streter and his group have been examining the effects of various levels of neural stimulation and inactivity on regulatory proteins and the myosin molecules in rabbit muscle. They have found that phasic stimulation at 60Hz for 2.5 seconds duration applied every 10 seconds for 5 weeks transformed fast twitch extensor muscles into slow twitch muscles by reprogramming the existing muscle fibers rather than by the appearance of new ones. The opposite transformation of muscle fibers (i.e., from slow to fast) occurred when various forms of hypoactivity and immobilization were applied to rabbit muscle. These results suggest that age-related changes in activity may result in formation of new populations or a modification of the functional characteristics of existing population of muscle fibers.

Endocrinology

The Endocrinology Section deals with a program of research on changes in endocrine function, regulation, and tissue responsiveness with age. Studies have been developed in appropriate animal models in order to define, quantify and link changes in endocrine functions with the expression of pathophysiologic processes associated with aging. Support of research on endocrinology and hormone dynamics in aging is important because of the many endocrine related changes associated with aging.

Benign prostatic hypertrophy (BPH) possibly is the most prevalent pathologic condition afflicting mature men in this country, yet reasonable accurate estimates of incidence and death rates do not exist. From autopsy series, it has been projected that perhaps 70 to 95 percent of all prostates in older men contain hyperplastic foci. Clinical information has suggested that most men over age 45 can expect to suffer from symptoms associated with detected hypertrophies. In some countries deaths attributable to BPH exceed those from prostatic cancer, reaching disturbingly high levels. The danger of mortality is from uremias and surgical procedures.

Although a variety of theories have been proposed to explain its occurence, e.g. neoplastic, arteriosclerotic, inflammatory, metabolic and nutritional, it is clear that the two major factors necessary for the onset of benign prostatic hyperplasia in men are the presence of the testes and aging accompanied by hormonal imbalances and other, as yet not understood, factors. There is a relative paucity of data and more research is needed to elucidate all aspects of the etiology of this disorder; nevertheless, there are several factors that strongly support the possiblity that benign prostatic hyperplasia is under endocrine control: 1) BPH does not occur in men who are castrated prior to puberty; 2) regression of esbalished BPH has been reported to occur following castration or treatment with antiandrogens; 3) biochemically, BPH is associated with an abnormal accumulation of the potent androgen dihydrotestosterone; and 4) in an animal model benign prostatic hyperplasia can be reproduced by hormones.

J.D. Wilson and associates, University of Texas, have established the following facts about the pathogenesis of prostatic hyperplasia in man and in dog model: a) dihydrotestosterone, the active intracellular androgen in the prostate of all species, accumulates in excessive amounts in the hyperplastic prostate; b) prostatic hyperplasia does not develop in the castrated male but does occur under circumstances in which estrogen formation in the aging male is increased; c) dihydrotestosterone accumulation is greater in the periurethral region of the human prostate where prostatic hyperplasia commences in the outer portions of the gland; d) plasma dihydrotestosterone levels are either unchanged or elevated in men with prostatic hyperplasia whereas plasma testosterone levels are lower in such men; and e) the plasma production rate of dihydrotestosterone is unchanged in men with benign prostatic hyperplasia whereas the production rate of testosterone is slightly decreased.

Considered together, these findings are consistent with the possibility that the accumulation of dihydrotestosterone is the cause of prostatic hyperplasia. However, it is not possible to be certain that the opposite is not the case, viz., that the accumulation of dihydrotestosterone in the hyperplastic gland is the consequence rather than the cause of the pathology. The problem of attempting to unravel cause and effect is particularly troublesome because of the difficulties in inducing prostatic hyperplasia in the castrated dog given androgens.

Significant progress in investigating the pathogenesis of benign prostatic hyperplasia has been made by J.D. Wilson. The successful technique for assessing the androgen receptor of the human prostate with natural binding ligands has shown that the receptor binds dihydrotestosterone approximately ten times as avidly as testosterone. This provides an explanation at the molecular levels as to why dihydrotestosterone and not testosterone is the effective intra-cellular androgen for prostatic growth.

In contrast to current belief, estradiol concentration is less in the hyperplastic than in the normal prostate of dog and man. This finding suggests that estradiol plays its major role in the early rather than the late phases of prostatic growth. Estradiol exerts its growth promoting action on the prostate directly, and the human hyperplastic prostate contains a high-affinity estradiol receptor protein similar to that found in the uterus.

A feature of prostatic hyperplasia is the fact that the condition could be induced in the castrate dog by the administration of dihydrotestosterone but not testosterone, the natural precursor of dihydrotestosterone in the prostate. This raised the possibility that some specific hormone of the testis, such as androstanediol or dihydrotestosterone itself, might be critical in the pathogenesis. Administration of long-acting testosterone to castrate dogs has demonstrated development of prostatic hyperplasia that can be prevented by the simultaneous administration of an inhibitor of the 5a-reductase enzyme. This prostatic hyperplasia is some metabolic feature of the prostate itself and not the result of a unique hormone of the testis.

Another feature of prostatic hyperplasia is that a higher concentration of dihydrotestosterone in the gland is required to induce its development than is required to saturate the androgen receptors. The reason for this is that large amounts of the hormone are present in the interstitial space and soluble fractions are in the stroma rather than in the epithelial cells. This raises the question as to whether the hormone component in the stroma may not be critical for development of prostatic hyperplasia.

Immunology:

The Immunology Program is concerned with research into the structure and function of antigens, various subsets of lymphocytes, monocytes and macrophages as well as mechanisms that regulate the aging immune system. It is anticipated that knowledge of the immune system generated by this program will identify causative factors as well as preventative or treatment measures for immunologically based disorders of the elderly. These include disease entities such as cancer, infectious diseases, rheumatoid arthritis and other autoimmune diseases of the elderly. It also includes the possibility that the immune system is a co-factor in the overall homeostatic regulation of tissues, organs and organ systems and, therefore, plays an important role in the age-related changes in these systems.

Research by Dr. Norman Klinman at Scripps Clinic and Research Institute (R01 AG01514) is aimed at evaluating the biologic characteristics of the B-cell population of aged individuals. He has examined various subpopulations of B-cells and the repertoire of expressed specificities. Dr. Klinman and his colleagues have collected several hundred monoclonal B-cell antibodies from spleen and bone marrow of aged subjects. They are now in the process of analyzing the fine specificities of these antibodies as well as the isotype potential of aged B-cells. Research from this laboratory has also shown that antibody specific immunosuppression can be transferred with T-cells but not with B-cells from aged individuals and that this occurs rather precipitiously between the 18th and 21st month of life in mice. Morever, these findings have been found to be true not only for responsiveness to the hapten dinitrophenyl (DNP) but also to an vironmentally abundant antigen, phosphocholine. Thus it appears that, while environmentally induced immunosuppression occurs both in the young and old, the age-related changes in the immune system may allow environmental contact to have a more profound effect later in life.

Studies of changes in cell function and cellular interactions are important to an understanding of the age-related changes in immune functioning. Dr. Tova Francus at Cornell University Medical Center (R01 AG/AI 01855) is using a cell transfer system in which liver or spleen cells from young donors were used to reconstitute syngeneic and allotypic congeneic lethally irradiated recipients. Recipients were then challenged with dinitrophenylated (DNP) bovine gamma globulin one day later and their sera were subsequently assayed for the presence of anti-DNP antibodies. Among other things, Dr. Francus has discovered that immature

B-cells from one-week old donors produce little or no antibody when challenged in a cell transfer recipient. However, they do produce a population of B memory cells. These findings indicate that the ability to produce memory cells develops earlier than the ability to produce antibody secreting cells in the primary response. Future work is aimed at expanding this approach to determine if the B-cell population of aged mice is deficient in its ability to establish and maintain itself in a cell transfer recipient as well as to respond to a challenge with T-dependent and T-independent antigens.

Some of the age-related changes in the functional capacities of B- and T-cell populations as well as in subpopulations may account for many of the immunologically derived diseases in the elderly. Dr. Parsottan Patel at the Trudeau Institute (R01 AG/AI 01234) has shown that the diminished ability of aged mice to resist infection from Listeria appears to be due to an impaired capacity of these mice to generate effective antibacterial specific immune mechanisms. These experiments showed that the peak protective T-cell production occurred at the same time in both young and old mice. A kinetics study of T-cell protective ability showed, however, that young donors transferred at least a thousand-fold more protection than similar cells from old donors. A limiting dilution analysis indicated that mediator T-cells from old donors were one-tenth as efficient in transferring adoptive immunity as cells from young donors. Dr. James Goodwin's research at the University of New Mexico (R01 AG 1245) on human subjects has shown further that B-cells from elderly individuals respond poorly to T-cell helper factor. Individuals over 70 years old respond with approximately 50% as much IgM and IgG as in cultures of B-cells from young controls. Thus, in these two instances it appears that the functional capacity of both B- and T- cells may be reduced with age. At the same time, however, research by Dr. Young Kim at Cornell University Medical Center (R01 AG 00842) suggests that not all B-cell functions are impaired with age. For example, when B-cells from young and old mice were challenged with sheep red blood cells, the number of plaque forming cells produced by the two age groups did not differ. This suggests that the binding charteristics of purified B-cells in the two age groups did not differ. Moreover, purified B-cells from old and young donors responded comparably when cultured with certain mitogens, suggesting again that these B-cell binding functions are not significantly impaired with age.

The influence of dietary restriction on lifespan has been known since the early 1930's. Research has progressed from these early studies to the present where investigators are attempting to understand the various mechanisms underlying the relationship between dietary restriction and immunologic functioning. One fruitful area of investigation has involved the influence of dietary restriction on the onset of autoimmune disease. In this regard, Dr. Roy Walford and his collegues at UCLA (R01 AG000424) have been investigating the influence of mid-life dietary restriction in long-lived mouse strains on immunologic functioning. Restriction beginning at 12, 16 or 19 months of age gives evidence of immunologic regeneration on a battery of five T- and B-cell mitogen tests as well as in response to injected sheep red blood cells as immunogens. Furthermore, mice restricted at mid-life have shown evidence of increased survival in comparison to controls. Finally, mice restricted at mid-life as well as those restricted at the time of weaning show a sharp reduction in incidence of autoantibody production after 24 months of age. This latter finding suggests that dietary restriction, even when it occurs at mid-life, may play an important role in reducing autoimmune disease.

There are other age-related effects of undernutrition that appear to have immuologic origins. One of these involves the genesis and growth of tumors. Dr. Edmond Yunis of the Sidney Farber Cancer Institute (R01 CA/AG 21084) has shown that a hypocaloric diet (i.e., normal mouse food given every other day) can delay the onset of tumors in C3H/HcJ mice and has prevented the occurence of tumors at 18 months of age in CBA/CaJ mice, a strain that normally shows high incidence of tumors at this age.

Several studies have undertaken to examine some of the mechanisms that are responsible for the effects of nutritional status on immune functioning. Two investigators, Dr. Margaret Heidrick at the University of Nebraska College of Medicine (R01 AG00904) and Dr. Gabriel Fernandez at the University of Texas Health Sciences Center in San Antonio (R01 AG/AI 0224), have independently been investigating the role of 2 mercaptoethanol (2-ME), an antioxidant. Dr. Fernandez has found a 400% increase in PHA proliferation of T-cells in aged B/W mice as compared to a 10% increase for young mice when cells are stimulated in the presence of 2-ME. Dr. Heidrick who has been conducting a longitudinal study of the short-lived BC3F strain of mice noted that, by 44 weeks, 2-ME fed animals had a significantly higher humoral response than animals fed a normal diet.

Another mechanism believed to be involved in the effects of dietary restriction on immune functioning is the production of prostaglandin E and F. Results from a study by Dr. Fernandez indicates that high calorie-high fat diets and high calorie-low fat diets are associated with increased levels of prostaglandin F in the lymph nodes of B/W mice. Only high calorie-high fat diets are associated with increased levels of prostaglandin E in the thymus. Because lymph nodes contain predominantly mature T-cells while the thymus contains immature T-cells, these results may indicate a differential influence of caloric and fat intake on prostaglandin induced suppressor activity associated with mature or immature T-cells.

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Contract Number: N01-AG-0-2100

Contract Title: Selection, Production, Characterization and Distribution of Genetically Marked Cells for Aging Research

Contractor: Institute of Medical Research, Camden, New Jersey

Projected Costs:

FY 1982: 240,941
FY 1983: 257,878
FY 1984: 275,895

Progress Summary:

The National Institute on Aging (NIA) Cell Culture Repository was established in 1974 to facilitate cellular aging research programs and to contribute to the elucidation of mechanisms in human aging at the cellualr and molecular level.

The contractor provides leadership in the acquisition, banking, and distribution of differentiated cell lines for use in aging research. The Repository contains cell lines from individuals who express aging associated degenerative processes. This includes premature aging syndromes, diseases with known or suspected DNA repair dysfunctions, neurological diseases associated with aging, and conditions which apparently predispose the cells to altered proliferative capacity in vitro. Cultures from well documented "cancer families" useful for comparative aging studies with diploid cultures from clinially normal individuals of various ages are also in the collection. The Repository also distributes the extensively banked normal diploid fetal lung fibroblast cultures, IMR-90 (human female) and IMR-91 (human male), which are available at various population doubling levels.

Skin fibroblast cultures from patients diagnosed as having Cockayne syndrome, Rothmund-Thomson syndrome and Werner syndrome are now available from the Repository which now contains 429 cultures for aging studies.

The Repository also contains a number of fibroblast cultures derived from males and females participating in the Baltimore Longitudinal Study at the NIA Gerontological Research Center (GRC). This is a long term in depth health study to acquire the scientific knowledge needed to understand the normal process of aging. The GRC cultures are dervived from individuals ranging in age from 29 to 96 and the in vitro lifespan of each culture has been estimated by the distribution of colony size (Proc. Nat'l. Acad. Sci. 75:1353, 1978). The availability of these cell lines of known proliferative potential from donors of various ages are an important new resource for biomedical and gerontological studies at the cellular level.

Research Contracts - BRCM

Office of Research Development

Contract Number: N01-AG-0-2101

Contract Title: Maintenance of a Long-Term Aged Rat Colony

Contractor: Charles River Breeding Laboratories, Inc.

Actual and Projected Costs:

FY 1982:	892,500
FY 1983:	1,047,500 (estimated)
FY 1984:	1,004,200 (estimated)

Progress Summary:

The objectives of this contract are to support the maintenance of a large colony of Fischer 344 rats and to distribute them on request to investigators supported by NIA. This colony has provided the primary support for aging research which uses the rat model of human aging. At the present time a large amount of data has been collected on this model and it serves as a very important standard by which to compare results obtained with other animals. Characterization of the strain is completed, and the results were published this year.

Proposed Course:

The evaluation of this contract, and the entire animal models program was completed this year. A recommendation for continuation with some modifications was given, the present contract was extended for three years, and a new overlapping, nine year contract will be awarded in December 1982.

Contract Number: NO 1-AG-7-2128

Contract Title: Development of a Colony of Multigenotypic Aged Mouse Strains

Contractor: Charles River Breeding Laboratories

Actual and Projected Costs:

FY 1982:	848,070
FY 1983:	859,070 (estimated)
FY 1984:	1,444,060 (estimated)

Progress Summary:

The objectives of this contract are to develop, define, maintain and distribute commonly used strains of laboratory mice to serve as model systems for aging research in the disciplines of immunology, neurobiology, pharmacology, nutrition, endocrinology, genetics and behavior. This colony was developed in response to investigators' requests for a number of different genotypes. The availability of the new strains was announced in NIH Guide for Grants and Contracts, Vol. 10, No. 6, 4/17/81. Characterization of the strains will be completed for all of the strains and will be published in early FY 1983.

Proposed Course:

The contract has been extended to allow for the recompetition process to be completed. No sources other than the present contractor were able to meet all contract requirements and it was reawarded to Charles River through FY 1985. Characterization of all strains is expected to be completed and the results published during FY 1983. A new nine-year contract, competitively awarded, is expected to begin in December, 1982. This contract will overlap the present contract for three years in order to maintain a constant supply of aged animals to NIA grantees.

Contract Number: NO 1-AG-9-2113

Contract Title: Caenorhabditis Genetics Center

Contractor: Curators of the University of Missouri-Columbia, Columbia, Missouri

Actual and Projected Costs

FY 1982: 41,130
FY 1983: 51,539 (estimated)
FY 1984: -0- Transfer to DRR

Progress Summary:

The objectives of this contract are to acquire, maintain, and distribute wild-type and mutant strain of *C. elegans* for biomedical research. The contractor will determine that these nematodes are free from contamination, and conform to visible phenotype discription, will conduct annual survival tests for new methods of storage, and will maintain and distribute the genetic map and nomenclature information. This colony is to be used primarily for investigators studying molecular genetics and developmental biology particularly as they impact on aging processes.

During the second contract year, the contractor has received strains from other laboratories, maintained an active schedule of distributions, developed and tested a computerized system for information retrieval, expanded strain distributions (double year 1) and revised the *C. elegans* genetic map.

Nearly 890 strains have been received and maintained. 361 total strains were distributed during year one of the contract.

Proposed Course:

The overall organization of the Center is appropriate and on schedule. The contractor has been providing services promptly as requested. This contract and colony has been evaluated and recommendations will be incorporated when appropriate and when the contract is renegotiated. The major recommendation was that this very worthwhile activity be transferred to a trans-NIH component, such as the Division of Research Resources in order to increase availability of its strains and bibliography.

Immunology Branch

Contract Number: N01-AG-9-2100

Contract Title: Longitudinal Study of Immune Function in Thymic Hormone-Treated Mice

Contractor: University of Alabama, Dr. Hiramoto

Actual and Projected Costs:

FY 1981: 111,037
FY 1982: 152,000

Progress Summary:

The objective of this contract is to determine the effect of thymic hormones on the development and aging of the immune system. Two studies were identified to evaluate the effect of four thymic hormone preparations in three strains of mice. In one study, a longitudinal one, mice would be periodically treated with thymic hormone throughout life and monitored every three months for immune function. In a second study, a cross sectional one, mice of various ages would be treated with the hormone preparations and periodically assayed thereafter for there effect on different immunologic functions and pathological conditions.

Results - As of the most recent progress report (January 1981) the following progress has been made: A/JN, CFW and C57BL/6 strains of mice have been evaluated longitudinally through 12, 14 and 16 months of age respectively and: 1 month old CRF, 1 month old C57BL/6 and 24 month old C57BL/6 mice were treated in the cross sectional study. The data from the cross-sectional are too meager to analyze. In the longitudinal study, each strain has been evaluated from four to six times. The mice have reached middle age and although some variations from the control groups has been observed, specific effects of the hormone treatment have not been observed in mortality, weight, hemotocrit, numbers of peripheral blood white cells, Coombs anti-red cell agglutinin titers, anti-red blood cells hemolysis and anti-nuclear antibody.

Proposed Course:

The workscope is being adhered to faithfully and the experiments are being performed on schedule. The contractor is conducting the study in a highly competent manner. The results are too limited to assess at this stage.

The contract will be modified for the FY 1982 year to include appropriate controls for the "nude" mouse studies to validate the data derived.

Report of Epidemiology, Demography, and Biometry Program

Overview of Epidemiology, Demography, and Biometry Program . . . EDBP-1
Overview of Epidemiology Office EDBP-2
Overview of Demography and Economics Office EDBP-19
Overview of Biometry Office EDBP-25

Overview of Epidemiology, Demography, and Biometry Program

National Institute on Aging

The Epidemiology, Demography, and Biometry Program (EDBP) of the National Institute on Aging (NIA) carries out research involving a diversity of problems related to aging and the elderly. This diversity reflects the program's organization around methodologic approaches to such problems rather than around their medical or social substance. Problems are selected for study on the bases of their relevance to the missions of NIH and NIA, and the likelihood that the application of the epidemiologic and population research methodologies in which the program has competence will be fruitful. The EDBP is divided into three working areas: epidemiology; demography and economics; and biometry. Although each EDBP research project falls under the aegis of one or another of these sections, most studies involve several staff members working cooperatively. The remarkable effectiveness of this teamwork represents one of the program's major strengths.

Research projects are either intramural, contract funded, or accomplished by interagency agreement. At the present time essentially all of the intramural projects represent secondary data analysis, i.e., research using data sets already collected by others at another time and usually for other reasons. Late in FY82 data will begin to become available for analysis from EDBP sponsored contract and interagency projects. As a result, a greater proportion of staff time will then be dedicated to analysis and publication of research findings than has previously been possible, i.e., these new data sets will become the basis of a major intramural effort even while many of the contracts and agreements continue.

Overview of Epidemiology Office

The FY82 achievements of the Epidemiology module in actuality represent the efforts of the entire EDBP staff, since such a major part of the achievements were related to the three Established Populations for Epidemiologic Studies of the Elderly (EPESE) (AG-0-2106, AG-0-2105, and AG-0-2107) and the National Health and Nutrition Examination Survey (NHANES I) Epidemiologic Followup Survey--all projects which have involved the total program staff.

Programmatic and scientific accomplishments related to the three EPESEs include the completion of primary interview instruments to be used at the three centers. This was accomplished by a questionnaire and an End-points Committee consisting of representatives from each center and staff of NIA. There was an internal review and OMB clearance of these instruments. Evaluation of the instruments was carried out at all three sites through limited pretesting. Restructuring of the interview instruments, and actual initiation of the data collection by household interview has begun. A Documentation Committee has been actively defining all criteria and methodology. As of June 1982, approximately one-third of the primary interviews had been completed and data tapes had been received from each of the centers. Limited tabulations of responses for the interviews completed for certain questionnaire items have been forwarded from the three centers as part of a centralized quality control strategy. A preliminary evaluation of the information received has already begun in anticipation of research to be carried out when the data sets are complete and final. A standardized telephone interview to be used at the first interim contact is currently under development with its common components agreed upon. Proposals for the first substudies have been submitted by the three centers. Currently under review are studies on adjustment to retirement, recovery from illness, and an algorithm for determining drug use, drug interactions and alcoholism. A Publications Committee comprised of members from NIA/EDBP and the three centers has met and arrived at working rules for the analysis and publication of results. These achievements represent the methodologic and administrative foundation for a multi-faceted research effort which will continue over the next several years.

FY82 accomplishments relative to the NHANES Followup population (Interagency Agreement AG-9-0018) also represent the efforts of several EDBP staff members. As a result of the cooperation of representatives from several Institutes, NCHS, and WESTAT (a primary contractor), basic instruments for interview and the basic methods for collection of hospitalization and death information were developed. The Institutes have been actively involved in the development, presenting hypotheses and the theoretical framework for an investigation. The questionnaires represent an integration of the research interests of all participating Institutes. Tracing of those persons who were examined 10 years ago began early in the year. At this time at least 82 percent have been located and agreed to participate. A major pretest of the followup interview was completed in May in the Philadelphia area, the results of which will soon be available. The actual collection of data for the main body of the study population will begin during July 1982. Although NIA remains the major supporter of this effort, the efforts of Dr. Joan Cornoni-Huntley (NIA/EDBP) and Dr. Jacob Feldman (NCHS) resulted in additional support being obtained from the National Cancer Institute; the National Institute of Arthritis, Diabetes, and

Digestive and Kidney Diseases; the National Heart, Lung, and Blood Institute; the National Institute on Allergy and Infectious Diseases; National Institute for Alcohol Abuse and Alcoholism; and the National Institute of Mental Health. The efforts of this past fiscal year have defined the methodology and initiated the actual activities which will eventually generate an enormous body of information for future analysis.

During FY81 a contract was awarded to Peter Bent Brigham Hospital/East Boston Neighborhood Health Center, an affiliate of Harvard University School of Medicine (AG-1-2106), to carry out a longitudinal, prospective study on the Natural History of Senile Dementia. The objective of this study will be to observe and describe the course of cognitive decline and general health in a group of SDAT victims and controls. The dementia cases will have been identified as a result of a community survey and most will not have been previously recognized as suffering from dementia. The objective of this study is to gain a better understanding of the prognosis and course of this disease among individuals first diagnosed while residing in their communities. Their illnesses are expected to be milder, less incapacitating, or earlier than is usual among patients coming to medical attention because of their dementia. Methods are currently being developed for the specific assessment techniques to be used in this study, prominently including methods of radiologic and psychoneurological assessment. The actual identification of cases and controls will not be accomplished until fall 1982.

The study of dementia in the Framingham Heart Study population (funded by inter-institute transfer of funds to NHLBI; 1-Y01-AG-2-0040-00) was initiated during FY82. An initial accomplishment was the inclusion in the current cycle of regular examinations of a screening test (the Folstein mini-mental status examination) and questions related to nursing home experience. This study represents a combined effort of investigators at NIA, NHLBI investigators, and investigators at Boston University (the contractor). A major aspect involves analysis of data on cognitive function performance collected during the 14th and 15th examination cycle, now 4 years ago. These data were generated by administration to the entire study cohort of a battery of eight cognitive function tests. They will be used for three essential purposes: a) to assist in the definition of a core group of patients with multi-infarct dementia (MID) and SDAT in order to search for factors involved in the pathogenesis of these illnesses, b) to define a group of patients who were functionally demented on the basis of this test, in order to carry out a study related to course and prognosis, and c) to define quantitative and qualitative aspects of cognition which may be characteristic of persons destined to develop dementia within the subsequent 4 years but who were not demented at the time of the examination. During the past fiscal year, NIA and NHLBI staff members have been actively involved in preliminary analysis of these data. Tentative findings have included the following: a) plots of scores from individual tests comprising the battery were neither normally distributed nor similarly distributed when one test was compared with another, b) factor analysis showed clear correlations between certain of the tests, a finding which may have special utility in the effort to determine predictors of dementia, c) examined individually, age, sex, and education all had major effects on test performance, d) controlling for education removed most of the apparent affects related to both sex and age. Current analyses of these data are focused on development of methods to allow cross comparisons of performance on the different component tests, the derivation of a composite performance score, adjustment for education, and standardization carried out in such a way that interactions between age, sex, and education are removed or controlled. While the major benefit of these methodological developments will be related to the objectives of the study defined above, they are also expected to provide population data on cognitive function for a defined cohort of older Americans.

During this fiscal year EDBP staff were actively involved in Epidemiologic Research on Hip Fractures using secondary data analysis methods. The first such study involved an analysis of data supplied by the District of Columbia Council of Governments related to hospitalizations for hip fractures. While this data set is of uncertain quality and completeness, it nevertheless allowed the estimation of age-specific incidence curves for hip fracture among elderly black females and elderly white females. The most remarkable result of this analysis was that the age-specific figures were very similar for blacks and whites until approximately age 74 when the incidence among white females became substantially greater than among black females. Peak incidence rates were reached for both blacks and whites at about 82 years of age with the rate among white women being approximately twice that among black women. A second preliminary study involved analyses of information available from NCHS's Health Interview Survey (HIS). While these data do not represent enough elderly black persons to allow derivation of age-specific figures for that racial group, they do allow the development of age-specific incidence curves for elderly white women, and for the comparison of age-specific curves according to education. These analyses suggest that the incidence is greatest among less extensively educated white females. The third avenue of research which has been explored utilized another NCHS data source, the Hospital Discharge Survey (HDS). This study, currently in progress, has more clearly defined the age-specific incidence curves for black American women and white American women than has ever before been accomplished. In general, the curves appear to substantiate a lower incidence of hip fracture at all ages among blacks as compared to whites, but suggest that this difference is of lesser magnitude (less than a two-fold difference) than has previously been supposed. When data from 5 years of the HDS were combined and logarithms of the age-specific incidences were plotted against age, approximately straight and parallel lines were observed for white females, black females, and white males. These curves are interpreted as implying that the risk for hip fracture in all three groups increased steadily, continuously, and exponentially with advancing age, tripling every 9 to 10 years. The essential difference among the three groups appeared to be one of intercept; equivalent starting points (age at equivalent baseline rates) were age 40 years of age for white females, 49 years for black females, and 48 for white males. This is taken to suggest that the underlying osteoporosis progresses at similar rates but either begins or becomes clinically significant at different ages according to age and sex.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 AG 02010 04 EDBP

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Followup of Health and Nutrition Examination Survey I (HANES I)

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	Joan Cornoni-Huntley, Ph.D.	Epidemiologist	EDBP	NIA
OTHERS:	Jacob A. Brody, M.D.	Associate Director for EDBP	EDBP	NIA
	Dennis Cosmatos, M.S.	Statistician	EDBP	NIA

COOPERATING UNITS (if any)
National Center for Health Statistics, Division of Analysis; NCI, Environmental Epidemiology Branch; NHLBI, Epidemiology and Biometry Program; NIADDK; NIMH; and NIAAA.

LAB/BRANCH
Epidemiology Office

SECTION
Epidemiology, Demography, and Biometry Program

INSTITUTE AND LOCATION
NIA, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.40	.20	.20

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The purpose of this project is to design and complete a followup of persons examined in the HANES I to study how factors previously measured relate to the health conditions that have developed since the survey. The three major areas for prediction of outcome are 1) nutrition 2) risk factors for chronic disease and 3) health care utilization. The survey will have a household interview including self-reporting of health conditions, utilization of health servics and behaviorial and social status plus some physical measurements as blood pressure, height, and weight. A feasibility study has been successfully completed to access cooperation. Tracing of individuals has begun and the pretest is to be completed in June 1981.
Outcome measures are defined as: morbidity, mortality, and institutionalization. All reports of hospitalization will be validated by obtaining copies of discharge summaries. First and last ECG will be obtained for hospitalization related to cardiovascular disease.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 AG 02031 03 EDBP

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)
The Impact of Living Arrangement and Family Structure on the Health of the Elderly

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	Joan Cornoni-Huntley, Ph.D.	Epidemiologist	EDBP	NIA

COOPERATING UNITS (if any)

Division of Analysis, NCHS

LAB/BRANCH
Epidemiology Office

SECTION
Epidemiology, Demography, and Biometry Program

INSTITUTE AND LOCATION
NIA, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The purpose of this project is to study health, social, and economic problems of the elderly related to different aspects of residential living and family composition. In particular, families including elderly persons who are functionally disabled will be compared with other types of families with and without elderly persons.

This project has been suspended because of lack of staff at both EDBP/NIA and NCHS. The NCHS is unable to accept any new interagency agreements.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 AG 02050 02 EDBP

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)
Systolic Hypertension in the Elderly (SHEP)

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	Joan Cornoni-Huntley,Ph.D.	Epidemiologist	EDBP	NIA
OTHERS:	William Friedwald, M.D.			NHLBI

COOPERATING UNITS (if any)
NHLBI

LAB/BRANCH
Epidemiology Office

SECTION
Epidemiology, Demography, and Biometry Program

INSTITUTE AND LOCATION
NIA, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Determine whether blood pressure lowering therapy reduces the rate of mortality from all causes of the occurrence of specified nonfatel morbid events in males and females 60 years of age and older with predominately systolic hypertension. The study is to evaluate whether treatment of isolated or predominately systolic hypertension in the elderly would decrease mortality. In FY82 this project was transferred to BRCM, NIA, because it is funded through the grant mechanism.

PHS-6040
(Rev. 2-81)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF** **INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 AG 02062 02 EDBP

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)
Patterns of Use of Prescription Drugs: Sleeping Medications

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	Lon R. White, M.D., M.P.H.	Medical Epidemiologist	EDBP	NIA
OTHER:	Jacob A. Brody, M.D.	Associate Director for EDBP	EDBP	NIA

COOPERATING UNITS (if any)

LAB/BRANCH
Epidemiology Office

SECTION
Epidemiology, Demography, and Biometry Program

INSTITUTE AND LOCATION
NIA, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.2	0.2	

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)
Study terminated without final conclusion because the data set was judged to be inadeuqate for the intended objectives.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 AG 02090 04 EDBP

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)
General Analysis of National Center for Health Statistics Data Systems

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	Joan Cornoni-Huntley, Ph.D.	Epidemiologist	EDBP	NIA
OTHERS:	Dennis Cosmatos, M.S.	Statistician	EDBP	NIA
	Jennifer Madans, Ph.D.			NCHS
	Joel Kleinman, Ph.D.			NCHS

COOPERATING UNITS (if any)
Division of Analysis, NCHS

LAB/BRANCH
Epidemiology Office

SECTION
Epidemiology, Demography, and Biometry Program

INSTITUTE AND LOCATION
NIA, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.30	.10	.20

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This interagency agreement allowed NIA to work cooperatively with NCHS in conducting analyses of appropriate data sets. The research topics included: 1) Major chronic conditions of the elderly and (2) the relationship between osteoporosis and the existence of fluoride in drinking water. Two papers are in process (1) TRENDS AND PREVALENCE RATES OF CHRONIC CONDITIONS IN THE ELDERLY U.S. POPULATION and (2) THE RELATIONSHIP BETWEEN HIP FRACTURE AND WATER FLUORIDATION: AN ANALYSIS OF NATIONAL DATA.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 AG 04001 02 EDBP

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)
Analysis of Functional Disability Data From Framingham Study

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	Lon R. White, M.D., M.P.H.	Medical Epidemiologist	EDBP NIA
OTHERS:	Jacob A. Brody, M.D	Associate Director for EDBP	EDBP NIA
	Joan Cornoni-Huntley, Ph.D.	Epidemiologist	EDBP NIA
	Manning Feinleib, M.D. DrPh	Associate Director for E&B	EBP DHVD NHLBI
	Robert J. Garrison	Chief, Biometrics Research Branch	EBP DHVD NHLBI
	A. Jette, M.D.	Boston University, School of Medicine	
	L. Branch, M.D.	Boston University, School of Medicine	

COOPERATING UNITS (if any)
NHLBI

LAB/BRANCH
Epidemiology Office

SECTION
Epidemiology, Demography, and Biometry Program

INSTITUTE AND LOCATION
NIA, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.2	0.2	

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Disability status of approximately 2800 surviving Framingham Heart Study participants was assertained. First description of the population is in press. Additional data analyses are currently in progress. The relationship between cognitive functioning and physical disability is being studied. Associations between disability, age, and work status are also being studied.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 AG 04003 02 EDBP

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)
Dementing Illnesses in the Framingham Heart Study

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	Lon R. White, M.D., M.P.H.	Medical Epidemiologist	EDBP	NIA
OTHERS:	Robert Garrison, M.S.	Chief, Biometrics Research Branch	EBP DHVD	NHLBI
	M. Feinleib, M.D., DrPh	Associate Director for EBP	EBP DHVD	NHLBI
	Jacob A. Brody, M.D.	Associate Director for EDBP	EDBP	NIA

COOPERATING UNITS (if any)
NHLBI

LAB/BRANCH
Epidemiology Office

SECTION
Epidemiology, Demography, and Biometry Program

INSTITUTE AND LOCATION
NIA, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.5	0.5	

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The Framingham Study population is being utilized for studies on dementia in the elderly. The major focus will be on: (a) a search for risk factors for the development of dementia, (b) the clinical course of persons who appear to have been demented when examined 5 years previously, and (c) a search for early evidence of illness in persons who were not demented 5 years ago, but who have become demented in the interim.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE
PROJECT NUMBER (Do NOT use this space)

U.S. DEPARTMENT OF
HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NOTICE OF
INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01-AG 04010 04 EDBP

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)
Catchment Area Study of Senile Dementia

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	Joan Cornoni-Huntley, Ph.D.	Epidemiologist	EDBP NIA
OTHERS:	William Eaton, Ph.D.		NIMH
	Ben Locke		NIMH

COOPERATING UNITS (if any)
National Institute of Mental Health
Center for Epidemiologic Studies

LAB/BRANCH
Epidemiology Office

SECTION
Epidemiology, Demography, and Biometry Program

INSTITUTE AND LOCATION
NIA, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.05	.05	

CHECK APPROPRIATE BOX(ES)
☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

In conjunction with NIMH, NIA is completing a study of senile dementia in an adult community population. A contract has been awarded to Yale University to survey a sample of the New Haven, Connecticut adult population for this purpose. NIA is specifically interested in defining the occurrence of senile dementia in persons 65 years of age and older. The study will consist of a household interview and a followup of all subjects. A questionnaire has been developed. The first wave of interviews was completed in 1981 and the second wave has just been completed. The final wave will be performed in the fall of 1982.

Publications: Eaton, W.W. et al: The Epidemiologic Catchment Area Program of the National Institute of Mental Health. Public Health Rep. 96: 319-325, 1981.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 AG 04014 03 EDBP

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)
Epidemiologic Studies of Alzheimer's Senile Dementia

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	Dennis Cosmatos, M.S.	Statistician	EDBP	NIA
OTHERS:	Peter Greenwald. M.D.	Health Research, Inc.		

COOPERATING UNITS (if any)
Health Research, Inc., New York State Department of Health
Division of Epidemioloy

LAB/BRANCH
Epidemiology Office

SECTION
Epidemiology, Demography, and Biometry Program

INSTITUTE AND LOCATION
NIA, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.05	.05	

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project aimed at the development of instruments, diagnostic criteria, and procedures necessary to conduct a planned, geographically based epidemiologic study of Alzheimer's Senile Dementia. With the help of staff from Health Research, Inc., methods to identify patients with senile dementia of the Alzheimer type (SDAT) were developed. Examination of the criteria most critical in the diagnosis of SDAT patients was made. The reliability and validity of the procedures developed was determined.

(Study completed in FY 81)

PHS-6040
(Rev. 2-81)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 AG 05001 02 EDBP

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)
Congestive Heart Failure and Digitalis Use

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	Lon R. White, M.D., M.P.H.	Medical Epidemiologist	EDBP	NIA
OTHERS:	Jacob A. Brody, M.D.	Associate Director for EDBP	EDBP	NIA

COOPERATING UNITS (if any)

LAB/BRANCH
Epidemiology Office

SECTION
Epidemiology, Demography, and Biometry Program

INSTITUTE AND LOCATION
NIA, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.2	0.2	

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)
Study terminated without final conclusion because the IMS data set appeared to be inadequate.

PHS-6040
(Rev. 2-81)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 AG 07010 02 EDBP

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)
Relationship Between Childhood Growth and Adult Blood Pressure (Feasibility Study)

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	Lon R. White, M.D., M.P.H.	Medical Epidemiologist	EDBP	NIA
OTHERS:	Mary E. Farmer, M.D.	Epidemiologist Trainee	EDBP	NIA
	George E. Comstock, M.D.	Johns Hopkins University, School of Hygiene and Public Health		

COOPERATING UNITS (if any)

The Johns Hopkins University, School of Hygiene and Public Health

LAB/BRANCH
Epidemiology Office

SECTION
Epidemiology, Demography, and Biometry Program

INSTITUTE AND LOCATION
NIA, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.5	0.5	

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Existing data from Washington County Health Study reviewed to determine feasibility of a larger study. In this preliminary study, no clear relationship observed between childhood habitus and adult blood pressure.

(Study completed)

CONTRACT

Name and Number: YALE UNIVERSITY (N01-AG-0-2105)

Title: Established Populations for Epidemiologic Studies of the Elderly (EPESE)

Date Contract Initiated: June 30, 1980

Current Annual Level: $400,000

Objectives: The purpose of this project is to conduct epidemiologic investigations in a community to develop new knowledge concerning the medical and social factors in health and diseases of the aged. Studies are to be completed on problems of pain, vision, hearing, sleep, drug use, constipation, social support and other pertinent areas.

Methods Employed: The project shall include cross-sectional and prospective studies in a carefully defined and accessible population using standard field and analytical techniques. Yearly surveillance of the population will be included.

Major Findings: During the first year, the demographic and social characteristics of each community have been reported. Also, a description of available health care facilities has been prepared. Extensive work is being done on development of the baseline survey. A section of this survey which includes information on chronic conditions, and social, demographic and psychological characteristics will be common to all centers. Pilot testing of this instrument is expected in June and July 1981 and will be followed by completion of the baseline survey.

Significance to Biomedical Research: The population over age 65 has been steadily increasing both in relative and absolute numbers. With this increase has come an awareness of a variety of health and social problems which are creating problems for our social and physical environment. It is important to have studies representing existing conditions in a community population. Within obvious logistical contraints populations will be available to the NIA scientific community for specific studies. High priority short term studies will be encouraged.

Proposed Course: A standardized telephone interview to be used at the first interim contact is currently under development with its common components agreed upon. Proposals for the first substudies have been submitted. A publications committee comprised of members from NIA/EDBP and the three EPESE centers has met and arrived at working rules for the analysis and publication of results. These achievements represent the methodologic and administrative foundation for a multi-faceted research effort which will continue over the next several years.

CONTRACT

Name and Number: UNIVERSITY OF IOWA (N01-AG-0-2106)

Title: Established Populations for Epidemiologic Studies of the Elderly (EPESE)

Date Contract Initiated: June 30, 1980

Current Annual Level: $700,000

Objectives: The purpose of this project is to conduct epidemiologic investigations in a community to develop new knowledge concerning the medical and social factors in health and diseases of the aged. Studies are to be completed on problems of pain, vision, hearing, sleep, drug use, constipation, social support and other pertinent areas.

Methods Employed: The project shall include cross-sectional and prospective studies in a carefully defined and accessible population using standard field and analytical techniques. Yearly surveillance of the population will be included.

Major Findings: During the first year, the demographic and social characteristics of each community have been reported. Also, a description of available health care facilities has been prepared. Extensive work is being done on development of the baseline survey. A section of this survey which includes information on chronic conditions, and social, demographic and psychological characteristics will be common to all centers. Pilot testing of this instrument is expected in June and July 1981 and will be followed by completion of the baseline survey.

Significance to Biomedical Research: The population over age 65 has been steadily increasing both in relative and absolute numbers. With this increase has come an awareness of a variety of health and social problems which are creating problems for our social and physical environment. It is important to have studies representing existing conditions in a community population. Within obvious logistical contraints populations will be available to the NIA scientific community for specific studies. High priority short term studies will be encouraged.

Proposed Course: A standardized telephone interview to be used at the first interim contact is currently under development with its common components agreed upon. Proposals for the first substudies have been submitted. A publications committee comprised of members from NIA/EDBP and the three EPESE centers has met and arrived at working rules for the analysis and publication of results. These achievements represent the methodologic and administrative foundation for a multi-faceted research effort which will continue over the next several years.

CONTRACT

Name and Number: PETER BENT BRIGHAM HOSPITAL (N01-AG-0-2107)

Title: Established Populations for Epidemiologic Studies of the Elderly (EPESE)

Date Contract Initiated: June 30, 1980

Current Annual Level: $300,000

Objectives: The purpose of this project is to conduct epidemiologic investigations in a community to develop new knowledge concerning the medical and social factors in health and diseases of the aged. Studies are to be completed on problems of pain, vision, hearing, sleep, drug use, constipation, social support and other pertinent areas.

Methods Employed: The project shall include cross-sectional and prospective studies in a carefully defined and accessible population using standard field and analytical techniques. Yearly surveillance of the population will be included.

Major Findings: During the first year, the demographic and social characteristics of each community have been reported. Also, a description of available health care facilities has been prepared. Extensive work is being done on development of the baseline survey. A section of this survey which includes information on chronic conditions, and social, demographic and psychological characteristics will be common to all centers. Pilot testing of this instrument is expected in June and July 1981 and will be followed by completion of the baseline survey.

Significance to Biomedical Research: The population over age 65 has been steadily increasing both in relative and absolute numbers. With this increase has come an awareness of a variety of health and social problems which are creating problems for our social and physical environment. It is important to have studies representing existing conditions in a community population. Within obvious logistical contraints populations will be available to the NIA scientific community for specific studies. High priority short term studies will be encouraged.

Proposed Course: A standardized telephone interview to be used at the first interim contact is currently under development with its common components agreed upon. Proposals for the first substudies have been submitted. A publications committee comprised of members from NIA/EDBP and the three EPESE centers has met and arrived at working rules for the analysis and publication of results. These achievements represent the methodologic and administrative foundation for a multi-faceted research effort which will continue over the next several years.

Overview of the Demography and Economics Office

The Demography and Economics Office has emphasized scientific work in population aging and macroeconomics as well as household studies of the well-being of the elderly. This effort has involved the completion of major research contracts on the Macroeconomic-Demographic Model (MDM) as well as the initiation of new research in health expenditures. Interdisciplinary work has been initiated in the area of age, work, and disability, utilizing the Disability Study in the Framingham population. The wealth of households is being studied across age cohorts with particular emphasis on the valuation of pension and social security benefits. These efforts will lead to various publications in the coming fiscal years.

The Demography and Economics Office has received two final reports entitled Model Description and Simulation Results. These have been used in our recent request for proposals on health expenditure modeling and will be edited into one book for publication. The research report on Projecting Alternative Futures for the Retirement Income System has been received and will be edited as a monograph for publication. The combination of these two reports represent a significant scientific achievement in providing information on NIA's research on the population aging. Underlying these reports is a complete, operational computer model that embodies a "base case" view of the U.S. economy and retirement income system for the next 75 years. The base case is consistent with all written reports as verified by our office. In addition, a User's Guide was completed which explains the computer operation of the model. As a measure of quality control, all aspects of the model have been saved on a tape that may be provided to other interested agencies upon request. These details are often overlooked in model development and stymie dissemination. The development of a "base case" has also permitted Dr. Anderson, project director, to testify before the Senate Select Committee on Aging. Drs. Cartwright and Anderson also presented research results to the NIA staff.

A major program achievement has been the development of a request for proposal on "Aging and Health Modeling." This effort involved briefing and coordination with such agencies as Health Care Financing Administration, Social Security Administration, Assistant Secretary for Planning and Evaluation, National Center for Health Statistics, and the the National Center for Health Services Research to ensure duplication and waste would not be created by our own effort. Under NIH Contract Office mandated small business set-aside, we have received two proposals. A scientific review committee has been formed for an evaluation on June 29, 1982, and we look forward to a FY82 award.

An interagency agreement (1-Y01-AG-2-0041-00) was signed with the Assistant Secretary for Planning and Evaluation to support grant research with the MDM. This research focuses on pension acceptance and the integration of the model with another large scale micro-simulation model of the Urban Institute. Projections of the retirement income system from both models will be compared for consistency. This research shall be part of a proposed pension modeling session at the December meetings of the American Economics Association. A proposed extension of this interagency agreement will result in a revision of the MDM labor market equations. That will begin this fiscal year and end in the next.

The Demography and Economics Office has also initiated a professional services contract with The Johns Hopkins University to receive a chartbook and graphic computer display on population aging and long-term care. This shall give us baseline information on the problem related to long-term care issues. This project will be completed in October 1982.

Our microeconomic research has been directed toward wealth studies. Obtaining the household survey of the President's Commission on Pension Policy, four public use tapes were transmitted to the National Technical Information Service and an additional set to the Department of Labor. Dr. Cartwright and Mr. Friedland prepared "Preliminary Research Findings of the President's Commission on Pension Policy" which was presented to the Workgroup on Wealth in Washington, D.C. As a result of that meeting, Mr. Friedland wrote a working paper, Valuing Pension Assets, to be distributed to the Work Group. Upon completion of the valuation of private pension wealth, we will be able to complete our paper on the distribution of wealth across age groups. Mr. Friedland is leaving us to take a position at Towson State University upon completion of his graduate student appointment.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 AG 01050 03 EDBP

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)
Age Structure in a Macroeconomic Model of the U.S. Economy

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	William S. Cartwright, Ph.D.	Economist	EDBP	NIA

COOPERATING UNITS (if any)

LAB/BRANCH
Demography and Economics Office

SECTION
Epidemiology, Demography, and Biometry Program

INSTITUTE AND LOCATION
NIA, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.0	1.0	

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A Demographic-Macroeconomic Model of the U.S has been developed. The impact of population aging will be examined on the nation's economy, retirement income system, labor force, and the welfare of the aged. The Demographic Macroeconomic Model represents the integration of eight models - Hudson-Jorgenson Growth Model, Anderson Labor Model, ICF Inc. Population Model, Social Security Model, Private and Public Employees Pension Model, Supplemental Security Income Model, and Medicare Model.

PHS-6040
(Rev. 2-81)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 AG 01055 01 EDBP

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)
Retirement Income System Research with MDM

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	William S. Cartwright, Ph.D.	Economist	EDBP	NIA
OTHERS:	Robert J. Rubin, M.D., Assistant Secretary for Planning and Evaluation			DHHS
	Thomas Gustafson, M.A.	Economist		DHHS

COOPERATING UNITS (if any)

LAB/BRANCH
Demography and Economics Office

SECTION
Epidemiology, Demography, and Biometry Program

INSTITUTE AND LOCATION
NIA, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: .10	PROFESSIONAL: .10	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The NIA enters into an agreement with the Assistant Secretary for Planning and Evaluation (ASPE) for the purpose of research on pensions, retirement, and labor force as well as issues involved in integration of micro and macroeconomic models. In FY83 we will support the revision and reestimation of the labor market model and simulation studies of the labor supply of the elderly.

PHS-6040
(Rev. 2-81)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 AG 01056 01 EDBP

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)
Age and Economic Activity

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	William S. Cartwright, Ph.D.	Economist	EDBP	NIA
OTHERS:	Robert B. Friedland, Professor Towson State University			

COOPERATING UNITS (if any)

LAB/BRANCH
Demography and Economics Office

SECTION
Epidemiology, Demography, and Biometry Program

INSTITUTE AND LOCATION
NIA, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: 1	PROFESSIONAL: 1	OTHER:

CHECK APPROPRIATE BOX(ES)
☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER
☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Study the relationship between age and economic activities so as to determine the life cycle nature of individual aging. This research will investigate areas of labor supply and health, saving behavior, and the economic well-being of the elderly.

PHS-6040
(Rev. 2-81)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 AG 01057 01 EDBP

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)
Planning Long-Term Care for the Elderly

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	William S. Cartwright, Ph.D.	Economist	EDBP	NIA
OTHERS:	Karen Davis, Ph.D. Professor, School of Hygiene and Public Health The Johns Hopkins University Baltimore, MD			

COOPERATING UNITS (if any)
The Johns Hopkins University School of Hygiene and Public Health

LAB/BRANCH
Demography and Economics Office

SECTION
Epidemiology, Demography, and Biometry Program

INSTITUTE AND LOCATION
NIA, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.10	.10	

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)
NIA will be provided with data from a computerized, interactive graphical display of long-term care in the health sector. The information on the future health needs of the elderly, resource requirements, cost, and economic implications will be particularly helpful to the Institute in its long-term care research planning.

PHS-6040
(Rev. 2-81)

Overview of the Biometry Office

The Biometry Office has continued this year in its participation in a variety of EDBP activities, in providing consultation on mathematical and statistical methodology to other groups within the program and in conducting research relevant to the mission of the program.

As FY82 has progressed, our involvement in the Established Populations for Epidemiologic Studies of the Elderly (EPESE) has increased substantially. Mr. Foley took an active role in overseeing the planning, preparation and submission of supporting statements for questionnaires submitted to the Office of Management and Budget for clearance of the baseline surveys of the three populations. Two site visits were made to the University of Iowa to evaluate progress in the sampling and fieldwork of the Iowa baseline survey--one visit in June 1981, before the survey began, and the other in June 1982, as the fieldwork was nearing completion. Dr. Brock has established and is chairman of the Documentation Committee for the three population studies. The function of this group is to evaluate and make recommendations for documentation of relevant scientific and procedural actions taken during the course of the studies. The committee's initial efforts will be concentrated on the design and conduct of the baseline survey. As telephone surveillance, mortality and morbidity followup and substudies are begun, the committee will make recommendations for appropriate documentation of those activities. Mr. Cosmatos has put considerable effort into the initial processing of the preliminary data tapes of the baseline survey received from the three centers. As we receive more data from these studies we expect to increase staff effort in data management and especially in consultation activities related to appropriate methodology for analysis of these data. To aid in these data management tasks we have placed Ms. Josephine Cruz in a statistical assistant position. In anticipation of the upcoming telephone surveillance Mr. Foley has developed a methodology package to be included in the supporting statements that accompany the telephone questionnaire to be submitted for OMB clearance.

The Biometry staff has assumed management of the Survey of the Last Days of Life. Because of personnel changes within the program, some aspects of this study have been modified to reflect more accurately the current interests of the program. The focus of the project now is medical and demographic rather than social and psychological. We wish to describe, for a sample of approximately 1,000 elderly decedents, the events and conditions present at the time of death. The following characteristics are of interest: location and time of death, state of consciousness of decedent, prior knowledge of impending death, presence of pain and use of pain-killing medication, and prior illnesses, disabilities and chronic conditions of the decedents. We also wish to study lifetime history of such conditions as dementia, deafness, blindness, paralytic stroke, hip fracture, Parkinson's disease, and lifetime admissions to nursing homes. The study will be conducted as a followback survey based on a sample of death certificates. To date contract proposals for the data collection have been reviewed with selection of a contractor and award to be made before the end of FY82.

Drs. Brock and Brody have been examining an expanded mortality data base covering the years 1900 to 1975 in 5-year intervals. Patterns in mortality by cause, age, and sex appear to show that the decline in mortality observed in recent years may have begun much earlier than previously thought, although the interpretation of these data must be viewed with caution, since the coverage and quality of the mortality data prior to 1935 has been subject to some question. Results of some of the mortality data analysis have been combined with population data from the Census Bureau and morbidity data from the National Center for Health Statistics for inclusion in two chapters written by Drs. Brock and Brody for forthcoming textbooks. The first is Principles of Geriatric Medicine, edited by Drs. Reuben Andres, Edwin Bierman, and William Hazzard, to be published by McGraw-Hill. The second is Handbook of the Biology of Aging, edited by Drs. Caleb Finch and Edward Schneider for Van Nostrand. Future work in mortality data analysis will include examination of the implications for the elderly population of continuing declines in mortality and the hypothetical effects of elimination of causes of death as well as improved statistical methods for studying age, period, and cohort effects in mortality data.

Our study of the effects of climatic extremes on mortality and morbidity in the elderly proceeds slowly. We have received from Sigma-Data Corporation, through our interagency agreement with the President's Council on Environmental Quality a data set which combines mortality data by county and climatic data originally coded by latitude and longitude, but converted to county codes. This geographic conversion, a complicated and time-consuming process, was completed relatively inexpensively through the interagency agreement. Mr. Cosmatos is now in the process of developing a measure for studying the association of mortality with climatic conditions taking into account time, temperature (number of days a specific temperature was observed) and the size of the population at risk within a given county. He will also conduct further mortality studies with climatic considerations such as deviations from normal temperatures, climatic time trends, and persistent duration of climatic extremes.

Mr. Foley and Dr. Cartwright have been collaborating on the development of data analysis based on the Framingham Disability Study. The data have been made available through an interagency agreement with NHLBI. The first study involves age, work, and disability.

Biometry staff have been involved in planning with NCHS and other agencies for a 1984 National Nursing Home Survey. As the frequency of these important data collection activities decreases, it is more important than ever to have strong input into those efforts which provide data most relevant for our program interests and needs for data.

Our interagency agreement with the Census Bureau ended during FY82. In the course of the project we received a number of valuable reports based on special analyses of census data pertaining to the middle-age and elderly populations. We expect to receive two additional reports as a result of this agreement--one containing methodological developments in mortality projection, the other an annotated bibliography on the demography of aging.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 AG 01070-02 EDBP

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)
Public Use Sample (1980 Census) for Aging Research

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	Charles F. Longino, Jr., Ph.D.	Department of Sociology
	University of Miami, Coral Gables, Florida 33124	
OTHERS:	Norfleet W. Rives, Jr., Ph.D.	University of Delaware
	Jeanne C. Biggar, Ph.D.	University of Virginia

COOPERATING UNITS (if any)

LAB/BRANCH
Biometry Office

SECTION
Epidemiology, Demography, and Biometry Program

INSTITUTE AND LOCATION
NIA, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project provided a proposal for the design and development of a research oriented public use sample data file from the 1980 U.S. Census of the elderly population. Technical specifications, including sample sizes, assignment of sampling weights, universe description, geographic coverage, and statistical reliability were given.

Final report received "A Proposal to Create 1980 Census Public Use Samples for Aging Research."

Project terminated.

PHS-6040
(Rev. 2-81)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 AG 01090 03 EDBP

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)
Demographic Aspects of Aging in the Older Population in the U.S.

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	Dwight B. Brock, Ph.D.	Statistician	EDBP	NIA
OTHERS:	J. Siegel	U.S. Bureau of the Census		

COOPERATING UNITS (if any)
U.S. Bureau of the Census

LAB/BRANCH
Biometry Office

SECTION
Epidemiology, Demography, and Biometry Program

INSTITUTE AND LOCATION
NIA, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The data will allow the impact of selective biomedical research which is age specific to be calculated for the elderly. The census analysis will indicate the magnitude of the elderly population and the growth in the size of the elderly population in all areas of the population in all areas of the nation by demographic and socioeconomic groups.

Publications: Current Population Reports Special Studies Series P-23, No. 111, Social and Economic Characteristics of Americans During Midlife. Washington, D.C., U.S. Government Printing Office, 1981, 54 pp.

Current Population Reports Special Studies Series P-23, No. 85, Social and Economic Characteristics of the Older Population: 1978. Washington, D.C., U.S. Government Printing Office, 1979, 44 pp.

Project terminated.

PHS-6040
(Rev. 2-81)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 AG 01161 02 EDBP

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)
Analysis of the 1977 National Nursing Home Survey Data

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	Dan Foley	Statistician	EDBP	NIA

COOPERATING UNITS (if any)

LAB/BRANCH
Biometry Office

SECTION
Epidemiology, Demography, and Biometry Program

INSTITUTE AND LOCATION
NIA, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

With the availability of the 1977 National Nursing Home Survey (NNHS) data tapes we are able to more clearly examine the health status of nursing home residents while controlling for specific variables such as senility, sleep disturbances, etc., which are of interest to the EDB staff and the Institute in general.

Publication: Liu, K., and Palesch, Y.: The nursing home population: Different perspectives and implications for policy. Health Care Financing Review. 3(2): 15-23, 1981.

PHS-6040
(Rev. 2-81)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 AG 01250 03 EDBP

PERIOD COVERED
October 1, 1981 to July 30, 1982

TITLE OF PROJECT (80 characters or less)
Michigan Data Archive - National Archive of Computerized Data on Aging

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	Dennis Cosmatos, M.S.	Statistician	EDBP	NIA
OTHERS:	Ronald Ables, Ph.D.		SBR	NIA
	Michael Traugott, Ph.D.	ICPSR/University of Michigan		
	Frances Jacobs, Ph.D.	Administration on Aging		

COOPERATING UNITS (if any)
Inter-University Consortium for Political and Social Research, University of Michigan

LAB/BRANCH
Biometry Office

SECTION
Epidemiology, Demography, and Biometry Program

INSTITUTE AND LOCATION
NIA, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.05	.05	

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The National Archive of Computerized Data on Aging (NACDA) is being developed within the framework of the Michigan Data Archives as a joint funding effort between the Administration on Aging and National Institute on Aging. Data contained in NACDA can be accessed by intramural research staff at NIA and analyses performed using the University of Michigan computer facilities. By using the Telenet communication lines and remote terminals to link with the Michigan Terminal System, analyses involving data on the health, social, economic, and demographic characteristics of the elderly will be interactively performed.

Terminated.

PHS-6040
(Rev. 2-81)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 AG 02064 03 EDBP

PERIOD COVERED

October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Trend in Drug Use Among the Elderly Population

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	Dennis Cosmatos, M.S.	Statistician	EDBP	NIA
OTHER:	Fred Eckel, M.S.	North Carolina Pharmaceutical Research Foundation		

COOPERATING UNITS (if any)

North Carolina Pharmaceutical Research Foundation (NCPRF)
Unversity of North Carolina at Chapel Hill

LAB/BRANCH

Biometry Office

SECTION

Epidemiology, Demography, and Biometry Program

INSTITUTE AND LOCATION

NIA, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: .05	PROFESSIONAL: .05	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

In conjunction with the North Carolina Pharmaceutical Research Foundation, NIA is conducting a study of drug usage by the elderly.

The Medicaid records for years 1973 thru 1976 will be the primary data source for this study. Questions on self medication, medical care factors, drug cost, and drug problems related to the elderly will be addressed.

PHS-6040
(Rev. 2-81)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 AG 02080 02 EDBP

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)
Secondary Analysis of HANES Predictive Factors

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	Dennis Cosmatos	Statistician	EDBP	NIA

COOPERATING UNITS (if any)

LAB/BRANCH
Biometry Office

SECTION
Epidemiology, Demography, and Biometry Program

INSTITUTE AND LOCATION
NIA, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.05	.05	

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

In preparation for the extensive follow-up survey for HANES I we anticipate completing preliminary analyses of the current baseline data. In particular the information on nutrition including dietary intake, food composition, and biochemistry will be analyzed to describe the status of the population at the time of the first examination. Through these preliminary analyses, subjects may be grouped into levels of nutritional intake or dietary behavior.

PHS-6040
(Rev. 2-81)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 AG 03010 04 EDBP

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)
Disease Specific Mortality Among the Elderly Population

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	Dwight B. Brock, Ph.D.	Chief, Biometry Office	EDBP	NIA
OTHERS:	Jacob A. Brody, M.D.	Associate Director	EDBP	NIA
	Dennis Cosmatos, M.S.	Statistician	EDBP	NIA

COOPERATING UNITS (if any)

LAB/BRANCH
Biometry Office

SECTION
Epidemiology, Demography, and Biometry Program

INSTITUTE AND LOCATION
National Institute on Aging, NIH

TOTAL MANYEARS: .30	PROFESSIONAL: .25	OTHER: .05

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A data base extending back to 1900 has been established to study trends and differentials in mortality rates of the elderly population by cause, age, sex, and race. Notable among the findings to date is that the decline in mortality observed in recent years may have begun much earlier than originally believed. These and other results are being published in a variety of places, in particular in chapters of two textbooks being published later this year.

Publications:

Brock, D.B., and Brody, J.A.: Statistical and epidemiologic characteristics of the United States elderly population. In Andres, R., Bierman, E.D., and Hazzard, W.R. (Eds.): Principles of Geriatric Medicine. McGraw-Hill, New York. In press.

Brody, J.A., and Brock, D.B.: Epidemiologic and statistical characteristics of the United States elderly population. In Finch, C.E., and Schneider, E.L. (Eds.): Handbook of the Biology of Aging (2nd edition). Van Nostrand Reinhold, New York. In press.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 AG 04013-03 EDBP

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)
Relationship Between Down's Syndrome and Alzheimer's Disease

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	Dennis Cosmatos, M.S.	Statistician	EDBP	NIA
OTHERS:	Irvin Emanuel, M.D.			

COOPERATING UNITS (if any)
University of Washington, Seattle, School of Medicine
Department of Psychiatry & Behavioral Sciences

LAB/BRANCH
Biometry Office

SECTION
Epidemiology, Demography, and Biometry Program

INSTITUTE AND LOCATION
NIA, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.05	.05	.05

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This study is to investigate the prevalence of Alzheimer's Disease in relatives of individuals with Downs's Syndrome. Patterns of familial aggregation of these diseases will be compared to their genetic models. The study will focus on 200 probands.

PHS-6040
(Rev. 2-81)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 AG 06000 03 EDBP

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)
Climatic Effects on Morbidity/Mortality in the Elderly

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	Dennis Cosmatos, M.S.	Statistician	EDBP	NIA

COOPERATING UNITS (if any)
National Climatic Center, NOAA

LAB/BRANCH
Biometry Office

SECTION
Epidemiology, Demography, and Biometry Program

INSTITUTE AND LOCATION
NIA, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.40	.40	

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Data on daily climatic conditions as reported from approximately 300 weather stations have been obtained from the National Climatic Center, and linked to daily mortality data for the period 1972 through 1977. An age-specific analysis of average daily mortality at various levels of climatic variables will be performed in order to ascertain relationships between age and climatic conditions. Climatic variables will include temperature, relative humidity, rapid changes in temperature, departures from normal temperatures, and sustained heat waves and cold fronts. Levels at which hypothermia and hyperthermia are more likely will be investigated in greater detail. Concomitant information on socioeconomic status and geographic location of the cases will also be considered.

PHS-6040
(Rev. 2-81)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 AG 06020 02 EDBP

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)
Health Effects of Environmental Pollutants on the Elderly (UPGRADE Project)

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I. Dennis Cosmatos, M.S.	Statistician (Health)	EDBP	NIA

COOPERATING UNITS (if any)
Presidents Council on Environmental Quality, Executive Office of the President

LAB/BRANCH
Biometry Office

SECTION
Epidemiology, Demography, and Biometry Program

INSTITUTE AND LOCATION
NIA, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: .10 (NIA)	PROFESSIONAL: .10 (NIA)	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Investigations will be made into the effects of environment on the health of the elderly. Interactions of environmental pollutants with climate variables will be investigated with respect to their effects on a variety of specific chronic conditions and mortality.

PHS-6040
(Rev. 2-81)

GERONTOLOGY RESEARCH CENTER

Report of the Intramural Research Program

Office of the Scientific Director GRC/OSD-1
Laboratory of Behavioral Sciences GRC/LBS-21
Laboratory of Molecular Aging GRC/LMA-35
Laboratory of Neurosciences GRC/LNS-48
Laboratory of Cellular and Molecular Biology GRC/LCMB-63
Clinical Physiology Branch GRC/CPB-72

Gerontology Research Center

Office of the Scientific Director

Administration

Administratively, the year found the Gerontology Research Center moving ahead in meeting its goals even in the face of tight budgetary restrictions. The GRC lobby, library, and OSD offices were refurbished with the new wall coverings, carpeting and library drapes helping to considerably brighten the facility's public areas. An effective procedure for controlling parking on GRC lots was initiated which has eased the parking situation for employees, visitors and BLSA subjects.

With the assistance of the Technical Development Section, a number of rooms were converted from office areas to provide much needed laboratory space. Work currently underway involves retrofitting GRC's cold and constant temperature rooms on several floors. An air balancing contract for the building is expected to be in place in the near future.

The Procurement Office has been tied into the NIH Information Management System (a computer system used in support of material management). This system has brought about a faster turn around time in payment of vendors, reduced the amount and flow of paperwork, and helped improve fund control and obligation accounts.

Technical Development Section

The Technical Development Section continues to provide maintenance and development services to support the scientific programs of the Center. Several new instruments were developed and our data processing facilities were substantially improved.

Practically all of the GRC's programs received support from the section's mechanical shops. Anion exchange filtration systems were fabricated for the Endocrine Section. For the Cardiovascular Section, an optical mount was designed for the video tracking of sarcomeres, and mouse mazes and chambers were built for the Psychophysiology Section.

Electronic instruments were developed to meet the special needs of several GRC programs. A precision calorimeter calibrator was built for the Biophysics Section. A multi-processor system to maintain several monkeys on operant conditioning schedules has been completed and is currently in its final checkout. Development was started for a system to track mice through 50 stations in a large and complex maze for the Laboratory of Behavioral Sciences. A means of transferring data, collected in the laboratory on floppy discs, to the central VAX computer system is almost complete.

The year since the installation of the VAX 11/780, has seen steady growth and acceptance by the many members of the staff at the GRC. It's popularity has grown to 40 users, and system utilization at the rate of approximately 50 hours of connect-time per day. In July, a major operations system revision was accomplished with minimal downtime and inconvenience to the users. In addition, system utility programs were developed in order to assist the users. BMDP, a widely used scientific subroutine package, was installed and is routinely used by the scientific staff. Newsletter and notice utilities were developed for the dissemination of information concerning the system. Another disk was installed which doubled its storage capacity. Remote terminal installation has continued throughout the building, requiring the installation of an additional 16 terminal ports.

In the coming year plans are to add additional memory to increase the system's speed, a high resolution graphics terminal and a letter-quality printer

Library

Even though the Research Librarian position, vacated in March 1980, remained unfilled, the Library Technician and two clerk typists were able to carry out their managerial liaison responsibilities while providing a full range of library services.

The Library's on line reference capability was strengthened by the addition of several new data bases, thus significantly increasing use of the MEDLARS and BRS system. With the first year of OCLC use completed, the fill rate for locating references improved substantially. OCLC implementation heightened cataloging efficiency and helped to speed up processing procedures for new acquisitions.

Use of the GRC Library by outside agencies and other libraries increased. Requests for information such as individually prepared bibliographies with emphasis on specialized subject matter, reader service inquiries, both written and by telephone, etc. showed a daily increase. Efficient interlibrary loan service continued with the ability to fill requests rising to 95%. The Library provides interlibrary loans to all the hospital libraries in Maryland and the District of Columbia, as well as to universities, colleges, and other government agencies. Currently, interlibrary loan requests average 150 or more per month.

A notable and so far, lasting improvement was made in the serial ordering process, namely, regular acquisitions of virtually all new titles in core series and in scientific/technical series are received by date of publcation as a result of library initiative for obtaining publications that are published annually or irregularly. Also, "standing order" arrangements were investigated with GPO and the GRC Library. This process provides timely receipt of items such as Cumulated Index Medicus, and unnecessary paperwork is eliminated. Eventually, savings in manhours and cost will be realized.

Animal Resources

This past year the Animal Resources Facility (ARF) faced many new challenges and again proved itself as an excellent resource of the Gerontology Research Center. The first order of business was the successful recruitment of another WG foreman to supervise the operation of the Wistar Rat Colony. As a result, production levels are now maintained at the maximum; husbandry and sanitation procedures also have shown great improvement. Due to severe budgetary cuts, the goal of making the Wistar Colony a TYPE III barrier colony was deferred. However, a modified TYPE IV barrier is still a workable alternative.

The facility came under the close scrutiny of two members of the American Association For Accreditation of Laboratory Animal Care (AAALAC). This was the second "on site" inspection the ARF has been faced with. To maintain accreditation the ARF must follow all the rules and provisions outlined in The Guide For The Care And Use Of Laboratory Animal Care. The inspection consisted of seven hours of direct inspection, plus review of animal husbandry procedures, quality control factors, and ethical procedures practiced throughout the animal colony. The ARF demonstrated complete adherence to the standards in the aforementioned guide and therefore maintained its full accreditation with AAALAC. The ARF-GRC is only the third NIH institute to receive and maintain AAALAC accreditation. The ARF sustained its institutional membership with both the national organization and the National Capitol Area Branch of The American Association of Laboratory Animal Science (AALAS).

To provide better care for the GRC animals, an animal technician training course is ongoing to instruct all the animal caretakers in all aspects of proper animal care. Upon completion of the course an examination was administered via the national organization of AALAS and the caretakers received national certification as an Assistant Laboratory Animal Technicians.

The ARF administrative staff continued to aid investigators in developing new techniques involving animals. Surgical and anesthesia skills were provided in over one hundred different procedures involving the use of primates, beagles and rodents. A new quarterly animal health report is being provided to the Scientific Director. These reports have indicated a substantial improvement in the health of GRC animals over the past year.

Comparative Nutrition Section

In earlier studies by the Comparative Nutrition Section, the activities of various enzymes were determined in two and seven month old female mice fed an adequate diet *ad libitum* or intermittently (every other day) or a diet containing low dietary protein (4%) *ad libitum*. The activities of these various enzymes were decreased in animals fed a 4 percent protein diet and intermittent-fasted an increased in the intermittent-fed animals. Further, it was shown that the mean values of the enzymatic activities of the intermittent-fed and intermittent-fasted animals were essentially the same as that of the *ad libitum* controls.

Recent studies, however, have shown that in animals subjected to these dietary regimes throughout their life span, the enzymatic activities of the animals fed intermittently were similar to the animals fed the low protein diet following twelve months of age. Thus, for the greater part of their life all dietarily restricted animals have a similar cellular enzymatic pattern indicating a common biochemical alteration supporting the hypothesis that dietary restriction increases life span by reducing protein synthesis and consequently reducing use of the genetic code.

Information Office

Highlights of GRC information activities include initiation of planning for the 25th anniversary celebration of the BLSA, extensive planning and work on NOVA's aging program, selection of tests and manning of GRC White House

Conference on Aging exhibit, completion of several special projects--BC/BS Worksite Blood Pressure Screening (100 people) and Red Cross Blood Drives, and more than 65 tours or lectures.

Charles Schaeffer, Changing Times magazine, attended last year's science seminar and used material extensively for an article on aging published in February. A number of other writers used information from the seminar for stories, including the Richmond Times-Dispatch, Philadelphia Bulletin, and Esquire.

The Information Office began planning for the 25th anniversary of the BLSA with Dr. Greulich appointing a committee chaired by the Communications Officer. To date, six full planning committee meetings have been held as well as a briefing for headquarters staff. A questionnaire sent to study participants elicited firm interest in attending the May 13-14, 1983 event from over 300 people. A site for the event has been selected and reserved, and program planning seems to be running well at this point.

NOVA's "Aging: The Methuselah Syndrome", aired in late March over PBS-TV, featured considerable footage and information on aging gleaned from the Gerontology Research Center. The entire project covered some eight months of consultation, several shooting dates, and coordination of volunteer participation and interviews with staff.

The NIH Health/Research Fair held at the WHCOA was an unqualified success with the most popular exhibit apparently being the GRC one which featured lung function and psychological tests used in Baltimore. Considerable planning, training, and man-hours were expended by information personnel in this endeavor.

International visitors toured/briefed included those from the following countries: Brazil (3); Japan (3); Great Britain; East Germany; Australia (3); People's Republic of China; Canada; France (2); Thailand (3); and, Yugoslavia. Other visitors came from the National Association of Social Workers, Provident Hospital, AARP, Howard University, George Washington University, University of Maryland, several community colleges, Montgomery County Senior Services, NIDR, and several Maryland high schools.

On the lecture circuit, the Communications Officer was keynote luncheon speaker for the Annual Conference of the Maryland State Evaluation Services, and gave two workshops for the Baltimore County Senior Conference. Two evening talks were given to students at Essex Community College and staff traveled to Deer Park, Overlea and Parkville Senior Centers to address older adults on research underway at GRC.

Two information personnel spent the past year helping to edit and process manuscripts, one on the BLSA and another on the NIA's exercise conference. Their excellent work in this endeavor resulted in an NIH Merit Award nomination for one staffer.

The office successfully handled 160 media inquiries and nearly 300 public inquiries. The total distribution of publications for these contacts, tours, lectures, seminars, and exhibits amounted to some 6,000. Considerable effort went into arrangements for videotaping of a children's program for cable television by Warner/Amex, and taping of the BLSA and a number of researchers for transmission to hospitals and medical schools by National Continuing Medical Education. Assistance was also provided to WCVB-TV (Boston), WHA-TV (Wisconsin), WTTG-TV (Washington), WJZ-TV (Baltimore), the BBC, and Canadian Broadcasting Corporation, and Japanese Television.

Other staff involvement the past year included serving on several NIH and GRC committees, editing Dr. Shock's chapter, "Longitudinal Studies of Aging in Humans" for the second edition of The Handbook of the Biology of Aging, and reviewing a movie script about life in a retirement community submitted by a New York writer.

Experimental Morphology Section

This section examines morphologic parameters important to aging and basic cell biology with research emphasizing morphologic techniques. The section's resources include transmission and scanning electron microscopy including Nomarski optics.

As a service facility, the section provides consultative and technical services including equipment maintenance and instruction in its use for projects which are described under other sections. These projects are as diverse as Dr. Joy Mohanty's (LCMB) use of darkfield optics for monitoring erythrocyte membranes to Dr. Donald Ingram's (LBS) analysis of data with our computer-digitizer to Dr. Mary Ellen Michel's (LNS) routine use of electron microscopes for studying permeability of the perineurium.

Other research efforts originate from within the section or are collaborative projects where we provide the morphologic expertise for projects of others. These efforts are described in this report.

GRC Information Office Activities FY 1982

Special Projects

1. Held 6 BLSA Anniversary planning meetings; briefing on same for Drs. Ringler/Butler; reserved hotel for event; chaired committee.
2. Prepared staff biographies for international E. German visit. Updated GRC Staff Profiles.
3. Publicized July 1981 Blood Drive.
4. Supplied photographs for exhibit and arranged for manning and equipment for BLSA demonstration tests at WHCOA; toured NIA volunteers for event.
5. Coordinated unique BC/BS Worksite Blood Pressure Screening program at GRC.
6. Chaired, publicized, organized GRC Red Cross Blood Drives for December 1981 and June 1982.
7. Consulted with 2 AARP staff members on lifestyle questionnaire and gave them leads for further details and tips.
8. Coordinated, arranged for subjects, advised on 3-day National Continuing Medical Education videotaping.
9. Advised and checked out for GRC investigator matter related to civil suit between vitamin companies.

Articles/Publications

1. Coordinated GRC section of annual directory/bibliography (December 1981).
2. Prepared copy for item on Geriatrics Continence Clinic to solicit outpatient referrals (Sunpapers, Senior Digest, Facts on Aging).
3. Prepared 6 articles for NIH Record (5 published).
4. JAGS article on incontinence in clearance.
5. News from NIH article on thallium scan submitted for publication.
6. Revision of "To Understand the Aging Process" considered, planned for 1982-83.
7. GRC IO staff processed/edited BLSA and Exercise manuscripts.

Newsletters

1. Researched, wrote and published 12 issues of GERON-NEWS.
2. Gathered background and published "Six S's News" for active BLSA participants, including letter and questionnaire on anniversary plans.

Reports

1. Prepared GRC OSD Program Review document.
2. Coordinated GRC portion of Annual Report; wrote OSD section.
3. Prepared GRC portion of 3 Director's Status Reports for NACA.
4. Researched and wrote GRC material for Annual International Activities Report (FIC).
5. Wrote GRC Director's Status Report for BSC.
6. Researched and prepared GRC submission for NBS Directory of Federal Laboratories.
7. Information Office kept and prepared minutes for all Branch/ Laboratory Chiefs, and Library Committee meetings.

Media

1. Consulted with WCVB-TV (Boston) on Alzheimer's Disease.
2. Arranged interviews and supplied background for DIAL Magazine aging story (published February 1982).
3. Worked with Beverly Orndorff Richmond Times-Dispatch on series of aging articles (published Fall 1981).
4. Arranged interviews and advised Pat McKewn for story in Philadelphia Bulletin (Fall 1981).
5. Lengthy preparations made for filming of NOVA segment and support material supplied for "Aging: The Methuselah Syndrome", aired March/April 1982.
6. Arranged interviews and supplied background for Kansas City Star editorial writer.
7. Set up taping of vital capacity test for "Prime Time" program over Channel 6 (Philadelphia) on Biomarkers Conference.
8. Worked extensively with and arranged interviews for John Tierney for Esquire article on aging (published May 1982).
9. Arranged interviews for Kathleen Sullivan of Querant Magazine (France).

10. Worked with Elliott Carlson on story for Dynamic Years (published May 1982).

11. Aided John Fialka in obtaining interviews; supplied followup background for Wall Street Journal article on BLSA (published March 13, 1982).

12. Organized BLSA volunteers/staff for children's cable television taping by Warner/Amex Cable for possible aging show.

13. Set up interview with Richard Cutler for WHA-TV (Wisconsin) documentary on biology of aging.

14. Supplied background and arranged interview with Dr. Greulich for Family Circle article on nutrition.

15. Began advising BBC and CBC-TV on Aging series.

16. Arranged BBC-TV filming of BLSA in June 1982.

Tours/Briefings

1. Toured BCH X-Ray Technician trainees (2 tours, 20 people).

2. Arranged 7 separate tours for Towson State psychology nursing, and physical education students (July 1981-May 1982).

3. Gave briefing and tour for GRC new employee orientations.

4. Briefed BCH dieticians on GRC programs; toured.

5. Baltimore Visiting Nurse Association social workers toured.

6. Hosted and toured PAHO official from Brazil and two other Brazilian physicians.

7. Toured/briefed Dr. Robert Luchi, Baylor Univ. College of Medicine.

8. Toured Japanese visitors from Tokyo Metropolitan Institute of Gerontology and another from Japanese Chemical Company.

9. Briefed and toured 9 Howard University students.

10. Toured WHO official, Dr. David Macfayden; later briefed GWU nursing students.

11. Jan Ehrman briefed and toured 3 foreign gerontologists from Australia, People's Republic of China and Thailand.

12. Held special briefing/laboratory tour for UMBC minimester students in gerontology.

13. Toured 11 NIA OPEA staff; Japanese visitor, Lansdowne High class.

14. Staff of Montgomery County Senior Services briefed/toured-two visits.

15. Univ. of Baltimore Psychology of Aging class visit to GRC.

16. Biology students from Univ. of Baltimore briefed.

17. Dr. S.D. Joseph of Australia toured the GRC.

18. Two Australian visitors toured; biology class from Centennial High (Columbia) briefed.

19. Hosted French Science Attache, Dr. Pinon, and NEI Visiting Fellow, Dr. Treton; toured Serbian Acad. of Sciences President, Dr. Banazir.

20. Toured two doctors from Thailand Ministry of Health; 20 Dundalk High biology students; toured 2 CCB students.

21. Arranged interviews and visit for Canadian physiatrist re: setting up gerontology center for Quebec.

22. Toured Baltimore-based staff of National Institute of Drug Abuse.

23. Briefed UM psychology class.

24. Briefed/toured Baltimore Summer Corps Newsletter staff.

25. Toured 21 Eastern Shore Hospital Center nursing trainees.

Outreach Education

1. Interviewed over WCVT-FM on GRC and NIA goals, programs (Dan Rogers).

2. Toured, briefed and lined up seminar attendance for 10 Univ. of Maryland Geriatric Rotation Residents.

3. Gave lecture to Essex Community College sociology of medicine class.

4. Advised and gave constructive suggestions to Rosemary Puhl for audiovisual material to be used in in-service training at Rossville Manor Care (nursing home).

5. Served as keynote speaker on "The Baltimore Longitudinal Study of Aging" at Annual Maryland Geriatric Evaluation Services Conferences.

6. Presented two workshops on the physiology of aging at Baltimore County Senior Conference (November 1981).

7. Provided kits containing a total of 400 publications to Dr. Edmund Beacham for Annual BCH Geriatrics Seminar.

8. Gave lecture to Essex Community College Psychology of Aging class and later held briefing/tour for another ECC class.

9. Set up laboratory sessions and recruited investigators for visit of 20 high school students participating in Maryland Academy of Sciences Junior Science Symposium.

10. Addressed 40 people at the Deer Park Senior Center (Reisterstown); 60 at Overlea Senior Center; and, 50 at Parkville Senior Center.

11. Represented NIA/GRC at National SPJ Distinguished Service Awards, Williamsburg, VA.

EEO Participation

1. Developed and researched GRC lobby display on handicapped for NIH International Year of the Disabled week.

2. Manned IYDP exhibit at National Society of Professional Journalists Convention (Washington, DC).

3. Conceived, arranged and maintained Black History Month lobby display; helped publicize month's cultural activities.

4. Helped revise/edit bylaws for GRC EEO Advisory Committee.

5. Communications Officer served on both GRC EEO Advisory Committee and NIH Handicapped Advisory Committee.

Employee Relations

1. Participated in NIA Secretary's Day; toured 40 people.

2. Held 2 employee seminars on savings options with NIH CU help.

3. Worked with Dr. Fleg to set up/publicize two staff CPR courses.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01-AG-00101-06-SCN

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Relation between Nutritional State and Aging

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	C. H. Barrows	Chief	SCN,OSD,NIA
Other:	G. C. Kokkonen	Chemist	SCN,OSD,NIA

COOPERATING UNITS (if any)

None

LAB/BRANCH
Gerontology Research Center, Office of the Scientific Director

SECTION
Section on Comparative Nutrition

INSTITUTE AND LOCATION
NIA, NIH, Baltimore, Maryland 21224

TOTAL MANYEARS: 2.0	PROFESSIONAL: 2.0	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Weanling male $B_6D_2F_1$/J mice were fed either: 1) a 24 percent protein diet; 2) a 4 percent protein diet; or 3) a 24 percent protein diet intermittently (fed Monday, Thursday, and 8 hrs. on Friday). Protein and enzymatic activities as well as DNA were measured in homogenates and various cellular fractions of liver. Both types of dietary restriction result in low cellular protein levels. However the activities of the enzymes were not consistently low in dietarily restricted animals; most likely due to specific regulatory mechanisms influenced by dietary manipulations. Three groups of C57BL/6J male mice, age 30 days, 14 months, and 20 months were fed diets containing either an amount of vitamins recommended by the National Academy of Sciences-National Research Council, one half this amount, four times this amount, or an amount of vitamins recommended by the American Institute of Nutrition. Mice, regardless of age, offered one half the RDA of vitamins began to die within two months and all were dead within eight months from the initiation of the study. At present the data do not indicate any beneficial effects from increasing the vitamins in the diet to four times the RDA.

PHS-6040
(Rev. 2-81)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01AG00151-03-OSD

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Aggregation Factor Visualized on Aggregating Cells

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	Susie Humphreys	Sr. Staff Fellow	EMS, OSD, NIA
Other:	Thomas Reese	Chief, Functional Neuroanatomy	LNNS, NINCDS, NIH

COOPERATING UNITS (if any)
NINCDS, NIH

LAB/BRANCH
Office of the Scientific Director

SECTION
Experimental Morphology Section

INSTITUTE AND LOCATION
NIA, NIH, Baltimore, Maryland, 21224

TOTAL MANYEARS: .3	PROFESSIONAL: .3	OTHER: None

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Sponge aggregation factor (AF), the large glycoprotein complex involved in species specific aggregation is the first aggregation factor to be visualized on the surface of aggregating cells. It apparently functions by a single macromolecule bridging between two cells with some arms extending to one cell and some to another. Many such linkages ligate adhering cells. It is a model of specificity of cellular interactions.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01AG00153-03-OSD

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Brush Border Ultrastructural Alterations with Ischemia

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	Susie Humphreys	Sr. Staff Fellow	EMS, OSD, NIA
Others:	Uzi Reiss	Visiting Fellow	LMA, NIA
	Bertram Sacktor	Chief, LMA	LMA, NIA

COOPERATING UNITS (if any)

LAB/BRANCH
Office of the Scientific Director

SECTION
Experimental Morphology Section

INSTITUTE AND LOCATION
NIA, NIH, Baltimore, Maryland, 21224

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0	0	0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Regeneration of the brush border of the proximal kidney tubule after isolateral ischemia has been monitored by transmission electron microscopy. The brush border takes longer to reform than does restoration of full activity of three enzymes (alkaline phosphatase, maltase, and γ-glutamyltranspeptidase) used as biochemical markers of brush border integrity.

This project has been inactive this year but is still viable. We await the compilation of the biochemistry by LMA investigators.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01AG00154-03-OSD

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Programmed Cell Death

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	Susie Humphreys	Sr. Staff Fellow	EMS, OSD, NIA

COOPERATING UNITS (if any)

None

LAB/BRANCH
Office of the Scientific Director

SECTION
Experimental Morphology Section

INSTITUTE AND LOCATION
NIA, NIH, Baltimore, Maryland, 21224

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.2	1.2	None

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Programmed cell death in gonadal cells of the nematode Panagrellus redivivus occurs in normal development and is genetically controlled. Regulation of programmed cell death may be a model for regulation of aging and death in organisms. We are studying the morphologic sequence of events involved in cellular death.

PHS-6040
(Rev. 2-81)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01AG00155-02-OSD

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Morphologic Analysis of Cardiac Muscle Used for Speckle Analysis

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	Susie Humphreys	Sr. Staff Fellow	EMS, OSD, NIA
Others:	Edward G. Lakatta	Chief, Cardiovascular Section	CPB, NIA
	Arthur A. Kort	Clinical Associate	CVS, CPB, NIA

COOPERATING UNITS (if any)

LAB/BRANCH
Office of the Scientific Director

SECTION
Experimental Morphology Section

INSTITUTE AND LOCATION
NIA, NIH, Baltimore, Maryland, 21224

TOTAL MANYEARS: 0	PROFESSIONAL:	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project has been terminated as it seems to have already answered the major questions of concern to the cardiovascular section.

PHS-6040
(Rev. 2-81)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01AG00156-02-OSD

PERIOD COVERED

October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Characterization of a Receptor to Palladin, the Aggregation Factor of Polyspondylium pallidum

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	Susie Humphreys	Sr. Staff Fellow	EMS, OSD, NIA
Others:	Steven Rosen	Associate Professor	Dept. of Anatomy Univ. of California at San Francisco
	Debra Drake	Research Associate	Dept. of Microbiology Univ. of California at San Francisco

COOPERATING UNITS (if any)

Departments of Anatomy and Microbiology, University of California at San Francisco

LAB/BRANCH

Office of the Scientific Director

SECTION

Experimental Morphology Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland, 21224

TOTAL MANYEARS: .5	PROFESSIONAL: .5	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Pallidin, a cell surface lectin implicated in mediating cell-cell adhesion in the cellular slime mold Polyspondylium pallidum, is inhibited by an endogenous factor which binds to it. The inhibiting factor, apparently a receptor, appears as a hemisphere. Pallidin binds all over the surface of the receptor like a fringe.

PHS-6040
(Rev. 2-81)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01AG00157-01-OSD

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Visualization of Al-binding DNA Crosslinks

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	Susie Humphreys	Sr. Staff Fellow	EMS, OSD, NIA
Others:	Steven Karlik	Staff Fellow	LCMB, NIA
	Gunther Eichhorn	Chief, Cellular and Molecular Biology	LCMB, NIA

COOPERATING UNITS (if any)

LAB/BRANCH
Office of the Scientific Director

SECTION
Experimental Morphology Section

INSTITUTE AND LOCATION
NIA, NIH, Baltimore, Maryland, 21224

TOTAL MANYEARS: .6	PROFESSIONAL: .6	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Double stranded calf thymus DNA binds to Al. When such DNA is heated to denaturation and then cooled, it remains together but is still single stranded according to NMR data (Karlik and Eichhorn). This linkage and the relative occurrence of the linkage should be reflected in the percentages of DNA which appear as "double strands" or linked and as single strands in the electron microscope. However, the traditional methods and the novel means we have devised of spreading DNA call for conditions (alkaline pH, presence of protein and/or foramide) which displace the Al. We are still searching for means which display the single stranded regions without displacing the Al. The binding of Al to DNA is of potential significance to aging if the claims of Pearl and Brody (Science, 208, 207-9, 1980) of Al concentration in nuclei in brains of Alzheimer's patients are valid.

PHS-6040
(Rev. 2-81)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF** **INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01AG000158-01-OSD

PERIOD COVERED

October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Protein Production in Rat Exocrine Submandibular Gland During Aging

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	Susie Humphreys	Sr. Staff Fellow	EMS, OSD, NIA
Others:	Bruce Baum	Clinical Director	NIDR

COOPERATING UNITS (if any)

NIDR, NIH

LAB/BRANCH

Office of the Scientific Director

SECTION

Experimental Morphology Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland, 21224

TOTAL MANYEARS: .1	PROFESSIONAL: .1	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

We are collaborating in a study to evaluate protein production in the exocrine rat submandibular gland during aging. We are evaluating ultrastructural features of the organelles involved in protein synthesis and processing in enzymatically dispersed cell preparations from young adult and aged male rats. Our colleagues at NIDR are measuring levels of protein production in these cells using radioisotopic methods and evaluating the nature of new protein synthesis by employing gel electrophoresis and autofluorography. Results demonstrate a diminution in protein production by cells from aged rats, in addition to some alterations in specific protein processing by old rat cells.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF** **INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01AG00159-01-OSD

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Epinephrine Binding Sites in Hepatocytes

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	Susie Humphreys	Sr. Staff Fellow	EMS, OSD, NIA
Others:	Elizabeth Dax	Special Expert	CPB, NIA
	Joseph Pitha	Chief, Macromolecular Chemistry Section	LCMB, NIA

COOPERATING UNITS (if any)

LAB/BRANCH
Office of the Scientific Director

SECTION
Experimental Morphology Section

INSTITUTE AND LOCATION
NIA, NIH, Baltimore, Maryland, 21224

TOTAL MANYEARS: .1	PROFESSIONAL: .1	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The amount of epinephrine binding in rat adipocytes and hepatocytes changes with age although the specific affinity for the receptor is constant. We want to determine whether these changes correspond to a change in the geometry of receptor distribution. By scanning electron microscopy and transmission microscopy of replicas, we will observe the binding of a ferritin-labelled antagonist, alprenolol, as a marker for epinephrine receptors. We have begun to devise proper manipulations for hepatocytes in suspension for morphologic observation and the conjugated antagonist has been synthesized.

PHS-6040
(Rev. 2-81)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF** **INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01AG00160-01

PERIOD COVERED

October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Cellular morphology, function and interactions in nerve.

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	N.L. Shinowara	Sr. Staff Fellow	EMS, OSD, NIA
Others:	J.M. Thompson	Sr. Staff Fellow	LN, NIA

COOPERATING UNITS (if any)

None

LAB/BRANCH

Office of Scientific Director, Gerontology Research Center

SECTION

Experimental Morphology Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, MD, 21224

TOTAL MANYEARS: 0.5	PROFESSIONAL: 0.5	OTHER: 0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A new project using morphological techniques, immunocytochemistry and tissue culture was begun to charaterize the cellular morphology, organization and function of nerves and to understand the cell interactions necessary to form and maintain nerve tissue during development and aging. The whole embryonic and adult chicken peripheral nerve was divided into two cellular compartments: the perineurial nerve sheath and the endoneurial contents which were studied as cultured explants for several days. Practically all of the explant cells had filaments that intensely stained with rabbit anti-chick fibroblast vimentin and were Colcemid sensitive. Cryostat sections of adult nerve had anti-vimentin staining in the epineurial and perineurial sheath cells, Schwann cells, but not axons. These vimentin-type intermediate filaments contribute to the characteristic large numbers of filaments observed by electron microscopy in the flat, adult perineurial sheath cells. Electron microscopy of rat sciatic nerve showed large increases in collagen and ground substance in the nerve sheath and endoneurium and increases in cytoplasmic inclusions in aging Schwann cells, sheath cells and axons.

PHS-6040
(Rev. 2-81)

LBS is making major contributions to the understanding of the role of behavior in the mediation of medical disorders. These contributions range from clinical intervention programs and normative behavioral assessments of clinically relevant issues to basic laboratory investigations. This year there are three sets of findings showing that behavioral techniques can be powerful therapeutic tools when used appropriately. Several years ago LBS scientists showed for the first time that it was possible to treat patients with chronic severe fecal incontinence to become continent by using a specific, rational behavioral procedure to teach the patients to control their anal sphincteric responses. In a study completed this year it was shown that patients born with a congenital defect of their spines (spina bifida) could be treated using combined behavioral procedures: toilet skills training was effective in improving bowel function at least 50% in 10/23 (45%) patients, 2 of whom (9%) became completely continent; sphincter training ("biofeedback") resulted in further significant improvement for 5 more and complete continence in 5 more. Thus, 15/23 (65%) were improved and 7/23 of these (30%) became fully continent. In our geriatric continence clinic where we see only patients 65 or older, we are obtaining comparable results not only with fecally incontinent patients but also with urinary incontinent patients. In the former group we have completed treatment with 9 patients: 8 of these were at least 50% improved and 3 of them became fully continent. Among the urinary incontinent patients 11 have completed treatment; 8 are at least 50% improved and 4 of them are completely continent. The third clinical intervention study completed this year was one designed to evaluate systolic blood pressure biofeedback and relaxation in the control of high blood pressure. These two behavioral methods have been shown in laboratory studies to be effective in lowering blood pressure: feedback by reducing peripheral resistance and relaxation by reducing cardiac output. Earlier findings had shown that patients who had received first feedback and then relaxation achieved pressures which were 14/10 mm Hg below baseline by the end of a six month treatment period. Follow-up studies carried out during a 6-mo post-treatment period showed that this effect was sustained throughout the follow-up period. Thus, patients who received the behavioral treatments could achieve and sustain reductions in blood pressure for at least six months. Furthermore, a number of patients who were receiving diuretic therapy to control their pressures were able to maintain reduced pressures for at least 9 months after discontinuing medication. On the basis of these findings we have proposed a BEHAVIORAL STEPPED CARE program to control blood pressure in patients with borderline or mild hypertension.

Several studies were completed this year which have looked at behavioral or personality characteristics either in patients or in normal populations. One interesting finding derives from the analysis of reaction patterns to various stimuli among normotensive subjects and hypertensive subjects. The data were collected in Sweden. However, the analyses were carried out at the GRC where the Swedish scientist now is a visiting foreign fellow. The analysis compared response patterns among several physiological measures recorded during each of 4 stimuli. The results showed that the hypertensive patients tended to emit response patterns which were more stereotypic than the normotensive controls. Furthermore, the patients' response patterns were characterized by a significantly greater incidence of maximal responses in blood pressure than was true for the normotensives. This finding replicated a finding first reported by Engel (Chief, LBS) in 1961. An additional finding from the present analysis was that beta-adrenergic blockade attenuated the magnitude of response of the hypertensive patients but neither reduced the response stereotypy nor reduced the tendency for maximal reactivity to occur in blood pressure. In a study reported by an LBS guest worker this year it was noted that chronic illness behavior (frequent visits to physicians, multiple somatic complaints and disabilities disproportionate to physical findings) is more likely to occur in people with irritable bowel syndrome than in people with peptic ulcers. These findings are based on a telephone survey of 832 people. Among the 67 (8%) people classified as manifesting irritable bowel syndrome and 84 (10%) who were categorized as having peptic ulcer disease, the findings indicated that the peptic ulcer people were similar to the general population on a number of indices of illness behavior (e.g., seeing a physician or otherwise treating a common cold overly seriously; complaints of acute illness; missing work because of acute illness); however, the irritable bowel syndrome people showed significantly higher incidences of these behaviors. Other findings suggested that illness behavior may be, at least in part, learned as a result of differential parental responses to childhood illnesses: People who report higher amounts of illness behavior also are more likely to report that their parents showed special consideration to them when they had colds or flu by giving them special foods, toys or other gifts. The notion that some life events (stresses) can precipitate medical illnesses is widely held to be true by workers in the field of psychosomatic medicine. However, this inference often is based on retrospective clinical reports which suffer from selection biases, or they are based on poorly designed questionnaires. A study completed by LBS scientists this year indicates at least 3 major sources of bias in these qustionnaires: 1) they include items related to physical health among the life stress indices; 2) they include items related to psychological adjustment (even though it is well-known that people with poor psychological adjustments are more likely to complain about illnesses); 3) they include items which are vague or subjective. When items reflecting these three sources of bias were eliminated from a life stress questionnaire given to 386 people, there was no relation between self-reported life stress and illness. However, when the biased items were included, the usual relationship between life stress and subsequent illness returned. These findings suggest strongly that the putative stress-illness relationship has been exaggerated and needs to be studied using procedures which are controlled for sources of bias. Daydreaming was studied in a group of 477 middle-aged women using a standardized questionnaire to assess daydreaming. The main finding was that the frequency of daydreaming was highest among women who evinced symptoms of psychological distress or who were medically ill. These findings offer further support to the notion that daydreaming is mediated by current concerns. Three studies utilizing the BLSA cohort have looked at the relationships of personality traits (extroversion, neuroticism or openness to experience) to adult development. One study showed that the personality dispositions of neuroticism and extroversion were major determinants of well-being in women. These results complement previous findings that these dispositions mediate well-being in men. A second study showed that people who are open to experience are more likely to make mid-life career changes than are people who are less open. Since the data from the BLSA files indicated that the openness was present prior to the career change, the findings suggest strongly that openness to experience may exert a causal role on this important feature of mid-life behavior. The last study in this series of reports from the BLSA showed that vocational interests were strongly related to the personality dispositions of extroversion and openness to experience. Men or women who were high in extroversion were more likely to choose social or enterprising rather than investigational careers; open individuals preferred artistic over conventional careers.

Several basic science studies of the relationships between behavior and physiological function were completed this year. One study examined the age differences of young (6-8 mo) and old (30-32 mo), C57BL/6 mice in response to subcutaneous injections of methadone. Dose-response analyses revealed that at higher drug doseages activity was increased. Time to peak activity was similar in the two age cohorts; however, the young animals had higher peak responses and the old animals responded for longer durations. Subsequent studies indicated that by one hour post-injection brain levels of drug were significantly greater in the old animals than in the young mice although plasma levels were similar. These age differences cannot be explained by differences in absorption, transport or metabolism. It is possible that the behavioral differences could be due either to age-related differences in distribution of the drug or to differences in numbers of opiate receptors. The influence of dietary carbohydrate was studied systematically in a cohort of genetically diabetic mice (C57BL/Ks - db/db) in a collaborative study between LBS scientists and scientists from Jackson Laboratories. These studies clearly established that these mice are carbohydrate-sensitive since it was shown that the age of occurrence of pathological effects of diabetes mellitus (hyperglycemia, islet cell destruction and death) was monotonically related to the amount of carbohydrate in the diet.

GRC has been one of the leading institutions in the world in the study of age differences in nigrostriatal, neuro-transmitter function. Previous research in this program had clearly shown that there were usually major age differences in behavior mediated by dopaminergic neurons in the nigrostriatal system. Systematic studies revealed that this age effect was, in part, mediated by a loss in dopamine receptors in older rats. Experiments done this year suggest strongly that this effect also is influenced by cholinergic receptors in the striatum. Three behaviors were studied following unilateral lesions in the substantia nigra: 1) turning to the ipsilateral side of the lesion; 2) sniffing and 3) grooming. The main findings were that: 1) indirect stimulation of the intact striatum with amphetamine caused increased turning, sniffing and grooming behavior in young (6 mo) and old (24 mo) animals. However, all behaviors were more prevalent in the young animals; 2) injections of dopamine produced increases in turning and sniffing but not in grooming. Once again the young animals showed dose-dependent enhancement which was significantly greater than that for the old animals; 3) atropine injections into the striatum caused dose-dependent increases in turning behavior in young animals but had no effect on old animals. Sniffing and grooming were unaffected; 4) finally, when atropine and amphetamine both were injected into the striatum, the young animals showed a potentiation of turning behavior while the old animals did not. Again, there were no effects on sniffing or grooming.

The program described above was developed and implemented by an LBS, Senior Staff Fellow who was nominated for conversion to tenure on the strength of his scientific accomplishments in this program and in our non-human, primate program. Because his conversion was denied, this individual left LBS for a responsible and well-paid position in private industry. Consequently, this will be the final report from LBS on the analysis of age differences in neurotransmitter function.

Scientists in LBS have been carrying out a number of experiments designed to identify further the mechanisms underlying the role of dietary restriction in longevity: It is well-known that rodents which are maintained on diets that are calorically restricted but are otherwise nutritionally adequate, will survive as much as 40% longer than ad libitum fed animals. One study utilizing short-lived (A/J) and long-lived (C57BL/6J) mice and their F1 offspring has shown that dietary restriction is not always beneficial to survival. Every other day feeding (EOD) was instituted in these 3 strains of mice at 1.5 mo, 6 mo or 10 mo post-birth, and these animals were compared to control groups fed ad lib (AL). All 3 groups showed increased survival when EOD was instituted at 1.5 mo; the C57 and F1 groups showed greater longevity when EOD was begun at 6 mo, but A/J survival was unaffected; finally, when EOD was introduced at 10 mo, the C57 and F1 strains were unaffected, but the A/J was adversely affected, i.e., mortality was increased. These findings indicate that there may be genetic mechanisms which are involved in the EOD effect. Several investigators have proposed that the EOD effect operates by prolonging the duration of growth, i.e., the growth rate. However, a study completed this year has shown that growth rate is correlated with lifespan only in AL rats but not in EOD animals. Thus, differences in growth rates appear only between groups but not within the EOD group. Exercise is another behavioral manipulation which has been reported to affect survival when it is introduced early in the lifespan. Since EOD animals also tend to be more active than AL animals, LBS scientists studied the relationship between EOD and exercise. Groups of rats aged 10.5 mo or 18 mo were housed in activity cages or standard cages. Half of the animals in each group were fed EOD and half were fed AL. The findings were that lifespan was increased 37% in the EOD, 10.5 mo group and was increased 13% in the EOD, 18 mo group. However, voluntary exercise was ineffective in prolonging lifespan in any group. Thus, these findings indicate that EOD can enhance survival in mature rats while exercise seems to have an early threshold. Clearly, exercise is not a necessary condition for mediating survival in EOD animals. Last year it was reported that 24 mo old, EOD rats have nigrostriatal dopamine receptor concentrations comparable to those of 3-6 mo old AL rats. Studies this year explored the interaction between dopamine and acetylcholine receptor activity on behavior in EOD animals. Just as in AL animals, there is evidence that these two systems interact: 1) Striatal injections of atropine produced dose-dependent increases in turning behavior and sniffing behavior in EOD, old (24 mo) and AL, young (6 mo) rats whereas old, AL animals showed no changes in turning behavior. Sniffing behavior showed similar effects, and grooming behavior was unaffected in all 3 groups. 2) When combined injections of amphetamine and atropine were injected into the striatum, only the young, AL rats showed evidence of potentiation of turning behavior. Turning behavior was unaffected either in the old, EOD animals or in the old, AL animals. Thus, these studies show that while EOD reduces differences between young and old rats in dopamine-mediated behavior and in acetylcholine-mediated behavior, when these two neurotransmitter systems are elicited simultaneously, it is possible to evoke age-related motor deficits. The loss of the principal investigator in this project (noted above) precludes any further investigation of this very interesting project.

A great deal of the research in LBS is directed at characterizing age differences in behavior, and at indentifying the mechanisms which mediate those differences. The range of these projects is very wide: it includes studies using human or animal models, and it includes laboratory experiments and questionnaire assessment methods. One project has utilized a standardized questionnaire to evaluate daydreaming. Findings from that project have consistently shown that self-reported instances of daydreaming decline with age. This year a laboratory study of vigilance has shown a similar effect; older subjects who are performing a vigilance task report fewer instances of mindwandering or daydreaming. A recently completed, questionnaire-based study looked at some of the relationships between self-reported, menopausal symptoms and other self-reported factors such as health status, interest in sex and a variety of demographic variables. Among the 396 women tested it was noted that frequency of sexual activity was mediated by the subject's attitudes and interest in sexual activity, and that women who were more sexually active tended to have fewer symptoms such as crying, fatigue or "hot flashes." Since some of these symptoms also reflect neuroticism, it will be interesting in future work to determine which symptoms are indicative of underlying personality traits and which symptoms are specific to the physiology of menopause. A number of laboratory studies have been carried out to determine some of the behavioral mechanisms mediating age differences in memory or problem solving. The effect of information content on memory was analyzed in one study. The findings were that even among very bright individuals over the age of 60 (college students), the ability to acquire information is inferior to that of younger subjects not only for unrelated material (e.g., words) but related sentences as well. A number of studies in LBS have shown that logical problem solving ability declines with age. In order to identify some of the mechanisms which mediate that ability (and perhaps to develop strategies to help older subjects maintain their proficiencies), LBS scientists have studied several mediating variables. One is to separate the problem into two tasks, analysis and synthesis. The hypothesis is that subjects who are having trouble solving difficult problems would benefit if they were required to obtain the information first (analysis) and then to have all of the analytic information available when they synthesized the solution. The results were surprising since separation of analysis and synthesis was most helpful to the better problem solvers when they were confronted with the most difficult tasks, but was not helpful to the poorer problem solvers. These findings suggest that the mechanisms used by good problem solvers to solve difficult problems are different from those used by poor problem solvers to solve simpler problems.

A number of studies in LBS are examining some of the basic behavioral and physiological mechanisms mediating age differences in performance. All of these studies have utilized rodent models, usually drawn from the GRC animal colony. One set of studies has studied age differences in thermoregulation in the mouse, and the effect of intracranial, electrical self-stimulation (ISS) on this process. The first study showed that body temperature in the mouse is stable until about 20 mo of age after which it falls monotonically throughout life. A visiting associate (formerly from the USSR) is exploring the role of ISS in cold tolerance. His findings to date show that 30 mo old mice which are allowed ISS 30 min/day for 3 wks have significantly improved cold tolerance relative to control animals or to themselves (in a delayed baseline, controlled experiment). Longitudinal studies of rodents sometimes control for breeding-behavior and other times do not. A study completed this year showed that 22 mo old, retired breeder, male, OBA/2J mice show poorer coordination and are less active than are virgin males. These findings suggest that breeding activity may in some way accelerate some aspects of physiological aging. Previous research in LBS has shown that older rats are less able to solve complex mazes than are younger animals. A study completed this year has extended this finding by showing that old mice also are less able maze solvers. Furthermore, the present study showed that the effect was present even when water deprivation rather than food deprivation was the motivating force. It is well-known that there are important behavioral as well as physiological differences between genetically obese mice (C57BL/6J ob/ob) and normal controls. Two studies designed to clarify some of these differences were completed this year. One showed that obese animals (which are similar to normal animals in their abilities to learn a response for a food reward) show lower resistance to extinction of a learned, appetitive response than do normal controls. This finding suggests that these animals have lower levels of hunger motivation than do matched controls. The second project showed that obese mice had higher resistance to extinction when the learned effect was a conditioned taste aversion to lithium chloride. This finding is consistent with the observations of others that this strain of mice is hyperreactive to taste stimuli. Two of the most commonly used mouse strains in aging research are the A/J (short-lived) and the C57BL/6J (longer-lived). A comprehensive study of various performance factors in 4, 10 and 24 mo old animals from these two strains showed that: 1) A/J mice were superior to C57 animals on tests of upper body strength; 2) C57 animals were superior in tasks requiring balance or movement; 3) C57 animals generally were more active; 4) A/J mice showed greater age deficits on most tests. These data provide further evidence that one needs to control genotype when evaluating age differences or age changes in motor behaviors.

Developments in the neurosciences have been exceedingly great over the last decade. These developments have led to increased collaboration between neuroscientists and behavioral scientists. This progression also has occurred at the GRC where LBS and LN investigators having been working together productively. Three of the collaborative projects which were completed this year have examined central neural enzymatic or transmitter concentrations in aging animals and correlated these neurochemical variables with behavioral functions. The neurochemical variables included choline acetyl transferase, glutamic acid decarboxylase and tyrosine hydroxylase; brain regions studied include several cortical and cerebral areas known to mediate motor behavior; the behavioral measures included performance in a radial maze (known to be an especially sensitive measure of hippocampal function) and a variety of measures of activity, strength or coordination. Since most of the studies were correlational and exploratory, and since there are a great many findings, the following results are primarily given to show the potentials of this program rather than to identify specific brain/behavior mechanisms: 1) In the radial maze there were profound age differences in behavior between young and old rats; after 15 trials the young animals had mastered the task whereas the old animals were still behaving at chance levels. The only age difference among the neurochemical measures was that old animals had a higher concentration of tyrosine hydroxylase than did young rats. However, other analyses revealed positive correlations between hippocampal choline acetyl transferase and maze performance in the old rats, and between cortical glutamic acid decarboxylase and maze performance in both age groups; 2) motor activity and neuroenzymatic activity was correlated only in young (4 mo) animals whereas strength and coordination was correlated with neuroenzymatic activity at all ages. Furthermore, the correlations between strength and coordination and neuroenzymatic activity were more numerous and tended to be higher in the oldest cohort (24 mo).

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01-AG 00062-09 LBS

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)
Daydreaming and Aging: Normative and Experimental

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	Leonard M. Giambra	Research Psychologist	LBS GRC NIA
Other:	Reginald Quilter	Electronics Tech.	LBS GRC NIA
	Jan Sinnott	NRSA post-doctoral fellow (sponsored by D. Arenberg) - now at Towson State University	

COOPERATING UNITS (if any)
None

LAB/BRANCH
Laboratory of Behavioral Sciences

SECTION
Learning & Problem Solving

INSTITUTE AND LOCATION
NIA, NIH, Baltimore, MD 21224

TOTAL MANYEARS: 1.1	PROFESSIONAL: .8	OTHER: .3

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The purpose of this work is to determine the parameters of spontaneous-thought-intrusions (daydreaming) and related mental activity such as insight, intuition, mindwandering, and curiosity. This is accomplished through the use of retrospective questionnaires and experimental manipulation. Topics of present interest are: (a) the lifespan changes in daydreaming in a longitudinal sample, (b) the relation of daydreaming incidence to tasks of varying vigilance requirements, and (c) the relation of sexual activity to menopause.

PHS-6040
(Rev. 2-81)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF** **INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 AG 00063-15 LBS

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Learned Modification of Visceral Function in Animals

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	J. A. Joseph	Senior Staff Fellow	LBS, GRC, NIA
Other:	B. T. Engel	Chief, LBS	LBS, GRC, NIA
	G. S. Roth	Research Chemist	CPB, GRC, NIA
	D. Ingram	Staff Fellow	LBS, GRC, NIA
	M. Talan	Visiting Fellow	LBS, GRC, NIA
	E. London	Senior Staff Fellow	LNS, GRC, NIA
	S. Waller	Staff Fellow	LNS, GRC, NIA
	L. D. Middaugh	IPA Fellow	LBS, GRC, NIA
	I. M. Kapetanovic	Senior Staff Fellow	LNS, GRC, NIA
	G. Hoffman	U. of Rochester, Dept. of Anatomy	
	D. Olton	Johns Hopkins U., Dept. of Psychology	

COOPERATING UNITS (if any)
Clinical Physiology Branch,
Laboratory of Neural Sciences
Johns Hopkins University School of Medicine
University of Rochester

LAB/BRANCH
Laboratory of Behavioral Sciences

SECTION
Psychophysiology

INSTITUTE AND LOCATION
GRC, NIA, NIH, Baltimore, Maryland 21224

TOTAL MANYEARS: 11.95	PROFESSIONAL: 4.80	OTHER: 7.15

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The purpose of this project is to investigate the role of the central nervous system in behavior. In some experiments monkeys (Macaca mulatta) are used to examine the extent to which the cardiovascular system can be modified by instrumental condiditioning. In other experiments we examined age-related changes in pre- and post-synaptic portions of various central neuronal systems of the rat and mouse using behavioral and biochemical analytical methods.

PHS-6040
(Rev. 2-81)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 AG 00064-21 LBS

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Problem Solving and Aging

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PIs:	David Arenberg,	Chief, Learning & Problem Solving Section	LBS GRC NIA
	Leonard M. Giambra	Research Psychologist	LBS GRC NIA
Others:	Jan Sinnott	NRSA, post doctoral fellow (sponsored by David Arenberg) - now at Towson State University	

COOPERATING UNITS (if any)

Baltimore City Hospitals

LAB/BRANCH
Gerontology Research Center - LBS

SECTION
Learning and Problem Solving Section

INSTITUTE AND LOCATION
NIA, NIH, Baltimore, MD 21224

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
2.1	.5	1.6

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The primary purposes of this project on aging are to: (1) identify reasoning processes; (2) determine how these processes change with age; and (3) develop techniques for reducing age deficits in reasoning performance. Reasoning is studied using problem solving procedures including concept learning and concept identification.

PHS-6040
(Rev. 2-81)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 AG 00065-22 LBS

PERIOD COVERED October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Verbal Learning and Age

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: David Arenberg	Chief, Learning & Problem Solving Section	LBS GRC NIA
Others:		
Elizabeth A. Robertson-Tchabo	University of Maryland	
Jan Sinnott	NRSA post doctoral fellow (sponsored by D. Arenberg) - now at Towson State University	

COOPERATING UNITS (if any)

Baltimore City Hospitals

LAB/BRANCH
Laboratory of Behavioral Sciences

SECTION
Learning and Problem Solving

INSTITUTE AND LOCATION
NIA, NIH, Baltimore, MD 21224

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
2.7	.5	2.2

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The primary purposes of this project on aging are to identify measures of learning and memory which change with age, to specify psychological processes and their relationships with age, and to develop procedures for improving learning and memory performance in the elderly.

PHS-6040
(Rev. 2-81)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF** **INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 AG 00066-21 LBS

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)
Perceptual Retention and Age

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	David Arenberg	Chief, Learning and Problem Solving Section	LBS GRC NIA

COOPERATING UNITS (if any)
Baltimore City Hospitals

LAB/BRANCH
Laboratory of Behavioral Sciences

SECTION
Learning and Problem Solving

INSTITUTE AND LOCATION
NIA, NIH, Baltimore, MD 21224

TOTAL MANYEARS: .9	PROFESSIONAL: .2	OTHER: .7

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The primary purposes of this project on aging are: (1) to investigate perceptual retention and interference; (2) to determine under what conditions age differences in retention are affected by interference; (3) to investigate processes of interference and perception; and (4) to describe age changes in nonverbal memory and identify correlates and predictors of these changes.

PHS-6040
(Rev. 2-81)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF** **INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 AG 00067-15 LBS

PERIOD COVERED
October 1, 1981 through September 30, 1982

TITLE OF PROJECT (80 characters or less)

Learned Modification of Visceral Function in Man

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	B. T. Engel	Chief, LBS	LBS, GRC, NIA
Other:	W. Whitehead	Guest Worker	LBS, GRC, NIA
	M. Schuster	Gastroenterologist	Balto. City Hospital
	W. F. Baile	Staff Physician	Balto. City Hospital
	P. T. Costa	Chief Stress & Coping Sec.	LBS, GRC, NIA
	J. Brinker	Dir. Cardiac Catheterization Laboratory	Johns Hopkins Hospita
	S. Middaugh	Guest Worker	LBS, GRC, NIA
	M. Fredrikson	Visiting Fellow	LBS, GRC, NIA
	K. L. Burgio	Staff Fellow	LBS, GRC, NIA

COOPERATING UNITS (if any)
Baltimore City Hospitals
The Johns Hopkins University School of Medicine

LAB/BRANCH
Laboratory of Behavioral Sciences

SECTION
Psychophysiology

INSTITUTE AND LOCATION
GRC, NIA, NIH, Baltimore, Maryland 21224

TOTAL MANYEARS: 6.95	PROFESSIONAL: 3.95	OTHER: 3.00

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project is concerned with the interaction of behavior and physiology in man. One study investigates behavioral procedures (relaxation and biofeedback) in the control of blood pressure in patients with high blood pressure; another study investigates the physiological mechanisms of heart rate control during exercise in normal man; one study investigates bowel function in normal man and patients with irritable bowel syndrome; another study is designed to learn whether patients with histories of meningomyelocele and/or urinary or fecal incontinence can be trained to become continent; one study investigates the behavioral and psychological characteristics of patients with angina pectoris who have been scheduled for coronary angiography.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 AG 00075-04 LBS

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)
Stress, Coping, and Personality in Aging Men and Women

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	Paul T. Costa, Jr.	Chief, Section on Stress & Coping	LBS	GRC	NIA
Other:	Robert R. McCrae	Senior Staff Fellow	LBS	GRC	NIA
	Alan B. Zonderman	IPA Fellow EOD 8/1/82	LBS	GRC	NIA

COOPERATING UNITS (if any)
1. Psychophysiology Section, LBS
2. Cardiovascular Section, CPP
3. Dept. of Psychiatry, Duke University Medical School

LAB/BRANCH
Laboratory of Behavioral Sciences

SECTION
Stress & Coping

INSTITUTE AND LOCATION
NIA, NIH, Baltimore, Maryland 21224

TOTAL MANYEARS: 4.5	PROFESSIONAL: 2.0	OTHER: 2.5

CHECK APPROPRIATE BOX(ES)
☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER
☐ (a1) MINORS ☒ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project is concerned with the effects of stresses, coping procedures, and enduring personality dispositions on psychological and health outcomes. One study investigates sex differences in life stress, personality, and subjective well-being; a second seeks to identify psychologically meaningful dimensions in MMPI responses from CAD patients and to predict from these dimensions the presence and severity of CAD as measured by coronary arteriography; a third measures personality through interviews and projective tests; a fourth utilizes longitudinal data to examine age-related constancy or changes in personality and personal adjustment; the fifth examines the effects of life event stress, personality, and biomedical status on health perceptions and illness complaints.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF** **INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 AG 00076-03 LBS

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Openness to Experience and Coping Styles

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	Robert R. McCrae	Senior Staff Fellow	LBS	GRC	NIA
Other:	Paul T. Costa, Jr.	Chief, Section on Stress and Coping	LBS	GRC	NIA

COOPERATING UNITS (if any)

LAB/BRANCH
Laboratory of Behavioral Sciences

SECTION
Stress and Coping

INSTITUTE AND LOCATION
NIA, NIH, Baltimore, Maryland 21224

TOTAL MANYEARS: 1.3	PROFESSIONAL: .5	OTHER: .8

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☒ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project is concerned with the personality dimension of openness to experience and its relation to coping styles. One study investigates alternative techniques for the measurement of openness, including self-reports and spouse ratings; a second study explores the relations between openness to experience and styles of coping and defense; a third study is concerned with developmental aspects of open dispositions in adulthood.

LABORATORY OF MOLECULAR AGING

The Laboratory of Molecular Aging has again had an outstanding scientific year. During FY 81-82 the Laboratory has continued to maintain a most prolific rate of productivity, *e.g.* 60 research papers and major reviews have been published, accepted for publication or submitted, all in high quality, peer-reviewed, scientific journals. Three of these papers represent major advances in their respective fields and have or will appear in the Proc. Nat. Acad. Sci. (USA). The Laboratory's research reflects a variety of individual as well as collaborative efforts both within and outside the Laboratory. They have brought credit and honor not only to the individual scientist, but also to the Gerontology Research Center, National Institute on Aging, as a locus for first-class, frontier-expanding, bio-medical research. These significant accomplishments have been achieved despite undercapitalization due to decreases by attrition in staff and severe restriction in other resources. Because of these cutbacks, propitious opportunities have necessarily been deferred and/or abandoned.

This report summarizes the following basic sciences projects: (A) Mechanisms of phosphate and calcium homeostasis, relation to senile osteoporosis and osteomalacia; (B) Pathophysiological and hormonal regulation of membrane transport systems; (C) Ion transport mechanisms; (D) Regulation of intermediary metabolism; and (E) Regulation of salivary gland function. In addition, the following clinical research project is described: (F) Studies on the oral physiological status of man during aging.

(A) Mechanisms of phosphate and calcium homeostasis, relation to senile osteoporosis and osteomalacia

Osteoporosis is a leading cause of mortality and morbidity in aging women. This prompted the Laboratory of Molecular Aging to undertake concerted research investigations on the mechanisms of phosphate and calcium balance as part of a major effort to understand the pathophysiological bases of senile osteoporosis and osteomalacia. Our approach, initiated in the previous year, was to define the mechanisms by which phosphorus and calcium are absorbed by the kidney and intestine and to determine how hormones, *e.g.* parathyroid hormone, calcitonin, glucocorticoids, and perhaps estrogen and prolactin; 1,25-dihydroxyvitamin D_3; diet; and chronic uremic syndromes induce specific alterations in the activities of the membrane transporters.

As noted in last year's Annual Report, the possible clinical use of Vitamin D_3 and its metabolites in postmenopausal osteoporotic women tends to obscure the fact that little is known about the function of vitamin D and in particular about its biochemical mechanism of action. To provide this needed information, we established a Vitamin D-deficient chick facility to produce animals to be used as our experimental model. Last year we described the effect of the Vitamin D status of the animal on the uptake of phosphate by kidney cells. This year, we showed the *in vitro* stimulation of phosphate uptake in isolated chick renal cells by 1,25-dihydroxycholecalciferol. We found that renal cells, isolated from vitamin D-deficient chicks, had an increased Na^+-dependent phosphate uptake when pre-incubated with 1,25-dihydroxycholecalciferol [1,25-$(OH)_2D_3$]. Phosphate uptake in the absence of Na^+ and α-methylglucoside uptake, dependent on Na^+, were not affected. Phosphate uptake was stimulated 15% by a 10^{-14} M 1,25-$(OH)_2D_3$. Maximal enhancement of 30% was obtained with 10^{-10} M. The uptake when fully stimulated by pre-incubation *in vitro* approximated the uptake of cells isolated from chicks that were previously repleted with 1,25-$(OH)_2D_3$, *in vivo*. Cells from repleted chicks were not stimulated additionally when pre-incubated with 1,25-$(OH)_2D_3$ *in vitro*. The increase in phosphate uptake could be measured after a one hour pre-incubation period; full response required at least two hours. Phosphate uptake induced by 1,25-$(OH)_2D_3$ was blocked by cycloheximide and Actinomycin D. Enhancement of phosphate uptake was relatively specific for the 1,25-$(OH)_2D_3$ analog of vitamin D_3 The potency order was 1,25-$(OH)_2D_3$>>25-$(OH)D_3$ = 1-$(OH)D_3$>24,25-$(OH)_2D_3$>>D_3. Kinetically, 1,25-$(OH)_2D_3$ increased the V_{max} of the phosphate uptake system; the affinity for phosphate was unaffected. [^3H]-1,25-$(OH)_2D_3$ was taken up by the isolated renal cells. It was estimated that the stimulation of phosphate uptake might be initiated by very few molecules of 1,25-$(OH)_2D_3$ per cell. It is proposed that 1,25$(OH)_2D_3$ contributes importantly to the mechanisms by which phosphate transport is regulated in the kidney. This pioneering study appeared in the June 1982 issue of PNAS.

The interactions of Vitamin D_3 metabolites and parathyroid hormone (PTH) is of crucial importance to phosphate and calcium homeostasis. This interaction was studied by examining the regulation of phosphate uptake in Vitamin D-deficient chick kidney cells by PTH. The activation by PTH of membrane-bound adenylate cyclase in cells from D-deficient chicks was decreased compared to the response in cells from D-repleted animals. Responses to other activators, *i.e.* prostaglandin E_1, GMP-PMP, NaF and forscolin, were not significantly different between -D and +D chicks. The blunted response of adenylate cyclase to PTH in D deficiency was due to a decrease in V_{max}, not a change in affinity. PTH had no effect on cAMP-dependent protein kinase activity in cells isolated from Vitamin D-deficient chicks, but the enzyme was activated by the hormone in cells from D-repleted animals. Incubation of cells from D-deficient chicks with PTH did not significant alter phosphate uptake. However, phosphate uptake by cells from +D chicks was decreased by the hormone. The transport effect was specific for the Na^+-dependent phosphate uptake system. Incubation of cells isolated from +D chicks with dibutyr cAMP mimiced the PTH effect on phosphate uptake. In contrast, cells from D-deficient animals were not effected by the cAMP analog. From these findings we propose two defects in Vitamin D-deficient chicks: (1) blunted response of adenyla cyclase to PTH; (2) blunted response of phosphate uptake distal to activation of adenylate cyclase.

Initial studies indicate that calcium uptake by duodenal mucosal cells from Vitamin D-deficient chicks was greatly enhanced after the isolated cells were incubated *in vitro* with extraordinarily minute quantities of 1,25-dihydroxyvitamin D_3. This finding establishes a new experimental model to examine the mechanism by which the vitamin/hormone regulates calcium transport.

It has been generally held that Vitamin D, like other steroid hormones, brings about its physiological effect by an interaction of the vitamin with intracellular receptors, transfer to the nucleus, and transcription of specific genes which code for transport proteins. Important experiments in our Laboratory now suggest an alternative mechanism. A model system was developed in which cholecalciferol (vitamin D_3) was incorporated into phosphatidylcholine liposomes and then the liposomes were incubated *in vitro* with isolated renal brush border membrane vesicles. The incubation resulted in an alteration of the phospholipid compositio the fluidity, and the transport properties of the membrane. The findings provide evidence consistent with the hypothesis that vitamin D_3 and metabolites modify membrane structure and function by "liponomic regulation."

Enzyme studies were continued on the regulation of synthesis of 1,25-dihydroxyvitamin D_3, the active form of Vitamin D. Isolated renal cells from Vitamin D-deficient chicks synthesized only 1,25-dihydroxyvitamin D_3 from 25-hydroxyvitamin D_3. When the chicks were repleted, the cells lost the ability to produce the 1,25-analog but formed 24,25-dihydroxyvitamin D_3 instead. Kinetic parameters for the 1- and 24-hydroxylase enzymes were determined.

Our studies on a parathyroid hormone-independent mechanism for the regulation of renal phosphate reabsorption made significant advances. The findings indicate: (1) phosphate infusion leads to a decrease in tubular reabsorption of phosphate in thyro-parathyroidectomized rats; (2) adaptation to phosphate infusion is expressed at the proximal tubule brush border membrane level as a decreased sodium-phosphate co-transport; (3) adaptation at the membrane levels preceeds the change in tubular reabsorption, perhaps suggesting an increased role for the distal tubule during a transitory phase of the adaptation; (4) alteration in phosphate uptake by the brush border membrane occurs within one hour of phosphate infusion by a parathyroid hormone-independent mechanism; and (5) regulation of phosphate reabsorption may be mediated by the serum phosphate level.

Important progress was made on our investigation of the mechanisms by which calcium is transported by the renal tubule. As reported last year, thermodynamic considerations would suggest that the transport of calcium from lumen to cell across the brush border membrane is down an electrochemical gradient and, therefore, mediated by a facilitated diffusion system. In contrast, movement of calcium from cell to blood across the baso-lateral membrane is against its electrochemical gradient and, therefore, would require an active transport process. Isolated baso-lateral membrane vesicles were found to possess an active calcium-sodium antiport system which would enable calcium to be pumped out of the cell in exchange for sodium entering down its electrochemical gradient. Kinetic parameters for calcium and sodium were determined for both influx and efflux systems. The transport system was shown to be membrane potential sensitive, indicating a stoichiometry of three or more sodium ions for each calcium ion. The pioneering and highly significant observation was made that parathyroid hormone increases the activity of the exchange. This finding may be the key to how the hormone works to enhance calcium transport.

(B) Pathophysiological and hormonal regulation of membrane transport systems

A novel discovery, reported last year, that glucocorticoids regulated specific transport systems in the kidney was explored further. Briefly, it was found that glucocorticoids, but not mineralocorticoids, increased amiloride-sensitive sodium-proton exchange activity (sodium uptake dependent on a proton gradient, inside>outside, and proton efflux dependent on a sodium gradient, outside>inside) in rat proximal tubule brush border membrane vesicles. Sodium uptake and proton efflux, independent of amiloride (a potassium-sparing diuretic), were not affected. Glucocorticoids also specifically decreased the sodium gradient-dependent phosphate co-transport system. These findings are consistent with the effects of glucocorticoids in stimulating acid secretion and causing phosphaturia in man and animals and may identify the locus of action and suggest the mechanisms by which the hormones act. This seminal investigation will be published in the PNAS.

Studies were continued in our exploration of the renal compensatory mechanisms that are invoked in chronic uremia or in pathophysiological states in which nephrons are lost, such as occurs in the aging process. The experimental animal model is the rat made uremic by the removal of one kidney and the ablation of two-thirds of the remaining kidney. It was found that sodium gradient-dependent phosphate uptak in brush border membrane vesicles from uremic rats was decreased relative to that from sham rats, when the animals were fed a normal phosphorus-containing diet. Uremic rats adapted to a low phosphorus diet by increasing phosphate absorption. When fed the low phosphorus diet the uptakes of phosphate by the membrane vesicles from uremic and sham rats were not significantly different. Because it was known that in chronic uremia parathyroid hormone levels are markedly increased, with devastating consequences on bone dissolution, the interactions of the hormone, diet, and uremic states on phosphate transport were examined. It was found that parathyroidectomy increased membrane phosphate uptake in uremic and sham rats, kept on a normal phosphorus diet, but the difference in phosphate uptake between the two rats still persisted. In contrast, when on a low phosphorus diet, parathyroidectomy did not increase phosphate uptake additionally in either sham or uremic animals. These findings suggest: (1) the decreased phosphate uptake in uremia is not attributable exclusively to a greater parathyroid hormone level; (2) the action of parathyroid hormone is blunted in animals on a low phosphorus diet; (3) uremic rats adapt normally to a low phosphorus diet; and (4) a low phosphorus diet can effectively reverse the phosphate transport decrement in uremic animals.

Brush border membrane sodium-proton exchange activity was stimulated in the remnan kidney model for chronic renal failure. These results are consistent with the known *in vivo* increase in acid secretion per surviving nephron.

Last year, we reported on the age-dependent changes in the molecular structure and activity of the renal brush border membrane, maltase, and the encouraging but preliminary attempts to develop specific antibodies to maltase. This year, monoclonal antibodies to maltase from young adult and aged rats were prepared by the hybridoma technique. Four cell lines producing antibodies of the IgG1 class to maltase were established. Two, designated 1F12E1 and 8B1G6, were specific for the catalytically active form of the enzyme found predominantly in enzyme preparations from young animals. Monoclonal antibodies, designated 7G10H3 and 2E1C10, reacted exclusively with an enzymatically inactive form of maltase found mostly in enzyme preparations from aged rats. The increased prevalence of an inactive form of the enzyme in the old rat accounts for the decreased maltase specific activity previously reported in the senescent rat. The active and inacti maltase species were separated by immunoaffinity chromatography using the monoclon antibodies as ligands. The separated forms of the enzyme were not distinguished by SDS-polyacrylamide gel electrophoresis. This study demonstrates for the first time the presence of an altered, antigenically distinct enzyme in senescent animal Critical issues on the mechanism of the aging process may be addressed by applicat of these findings. This important gerontological research investigation has been submitted to PNAS.

Studies were initiated on the effects on diabetes and insulin on renal transport systems. Our animal model is the streptozotocin-treated rat. Streptozotocin rapidly and selectively destroys β-cells of the pancreas and the animals present a condition resembling diabetes mellitus. Preliminary results on the effects of diabetes on membrane transport systems are most interesting and specific age-dependent alterations are suggested.

Glutamine is the most prevalent amino acid in human plasma and is the major source of urinary ammonia. Thus, it represents a crucial metabolite in the regulation of acid-base balance. Because *in vivo* data suggest that glutamine fluxes across the proximal tubule brush border and baso-lateral membranes may change during metabolic acidosis, a study of the mechanisms and regulations of glutamine transport in the isolated vesicles were initiated. It was found, to-date, that uphill glutamine uptake by brush border membrane vesicles was energized by both a sodium electrochemical gradient and a membrane potential, inside negative. The sodium-glutamine co-transport system was electrogenic, depolarizing the membrane. The glutamine transport system was stereospecific and not shared by glutamate, basic amino acids, proline and glycine. Several neutral amino acids share the system. Glutamine uptake was sensitive to pH but was not affected by ammonium.

In a continuing examination of other amino acid transport systems in the kidney it was found that glycine was concentratively taken up in renal brush border membrane vesicles, energized by the sodium electrochemical gradient. The system was characterized for kinetics and specificity. It was concluded that a single transport system for glycine is present in the brush border membrane and that it functions to reabsorb glycine by a carrier not shared by the other classes of amino acids.

Established kidney cell lines (LL-PK) and primary cultures derived from chicks were used to examine cellular transport systems and their hormonal regulations. Correlations were established between the actions of various hormones, *e.g.* parathyroid hormone, vasopressin, glucagon and isoproterenol, on adenylate cyclase and protein kinase activities and the effects of these hormones on metabolite uptakes. Special attention was given to the action of forskolin, a recently reported diterpene with exceptionally potent ability to stimulate adenylate cyclase. Chick cell adenylate cyclase was stimulated 10-fold, causing complete activation of protein kinase. At low concentrations, forskolin markedly potentiated the action of parathyroid hormone. The affinity of the receptor for parathyroid hormone was not shifted. Forskolin mimicked the actions of hormones in elevating cAMP and inhibiting phosphate uptake in the renal cells.

Studies on how hormones, neurotransmitters and pharmacological agents effect phosphatidylinositol turnover, calcium flux, potassium release, amylase secretion, and adenylate cyclase and protein kinase activities in the rat parotid acinar cell aggregate were continued. It was found that chlorpromazine, by itself, greatly stimulated glycerophospholipid metabolism; had little effect on basal-, isoproterenol- and substance P-stimulated amylase secretion; and inhibited the secretion induced by carbamylcholine. The drug also inhibited epinephrine-stimulated phosphatidylinositol turnover and potassium release in a manner consistent with known inhibitory effects on receptor binding. Carbamylcholine actions on phospholipid turnover and potassium release were not changed with age of the rat (3 mo vs 24 mo).

(C) Ion transport mechanisms

The mechanism of Ca^{2+} translocation in sarcoplasmic reticulum was investigated using fast kinetic methods. Results of these studies indicate that the translocation mechanism involved rapid transfer of Ca^{2+} from an external binding site to an occluded site prior to its release at the inner membrane surface.

The kinetics of the phosphoenzyme intermediate reactions of the electric organ (Na,K)-ATPase were compared in the presence and absence of K^+. Results indicate the presence of K^+-activated acceleration of the interconversion reaction favoring a mechanism involving simultaneous occupation of Na^+ and K^+ transport sites. Examination of the initial turnover characteristics of the purified kidney

(Na,K)-ATPase provided additional support for a simultaneous transport mechanism.

The enzymatic partial reactions of the cardiac myofibrillar ATPase were examined with respect to Ca^{2+} sensitivity. Preliminary results indicate the presence of regulation of the steady state rate involving Ca^{2+}-activated release of reaction products.

(D) Regulation of intermediary metabolism

These studies seek to define and describe the molecular mechanisms whereby the major catabolic (*i.e.* energy-releasing) pathways of intermediary metabolism are controlled, and to investigate the ways in which these controls are altered in old-age. Current investigations feature: (1) the control of pyruvate dehydrogena and α-ketoglutarate dehydrogenase activities by micromolar concentrations of Ca^{2+} ions; (2) the transport of Ca^{2+}-ions into and out of heart mitochondria and its relation to the homeostasis of cytosolic free Ca^{2+} concentrations; (3) the control of pyruvate dehydrogenase in skeletal muscle mitochondria and the effect of fatty acid and ketone oxidation; and (4) the impact of aging upon the transfer of cytosolic reducing equivalents into heart mitochondria by means of the malate/aspartate shuttle.

The α-ketoglutarate dehydrogenase of intact rat heart mitochondria was activated by Ca^{2+}, with 50% activation at approx. 0.5 nmol of total Ca^{2+}/mg of mitochondrial protein, in the presence of inorganic phosphate and Mg^{2+}. Mitochondrial Ca^{2+} contents in excess of 2 nmol/mg of protein resulted in 100% activation of the enzyme. Investigation of Ca^{2+} release from the mitochondria using the metallochro indicator Arsenazo III defined a $S_{0.5}$ of 5.4 ± 0.4 nmol of Ca^{2+}/mg of protein, whe the endogenous Ca^{2+} content of the mitochondria was progressively depleted with EGTA, prior to the initiation of the release process being studied. The subsequen determination of matrix free Ca^{2+} concentration by the "null-point" technique allo expression of these results in terms of free concentration rather than Ca^{2+} conten with an activity coefficient of approx. 0.001 for matrix Ca^{2+}. From the above, Ca^{2+} efflux from heart mitochondria was not saturated at the mitochondrial Ca^{2+} contents or concentrations which gave effective regulation of dehydrogenase activi A consequence is that heart mitochondria do not buffer the pCa of the extramitochondrial medium at these Ca^{2+} contents (<2 nmol/mg of protein) and this was shown in direct measurements of extramitochondrial pCa. This is taken to question the physiological significance of mitochondrial buffering of cytosolic free Ca^{2+} in normal heart.

In studies on the effect of senescence on Ca^{2+}-ion transport by heart mitochondria it was found that both the rate of uptake of Ca^{2+} into isolated rat heart mitochondria and the rate of release of Ca^{2+} by a separate, Na^{+}-dependent, pathway were shown to be diminished in senescence (24-month relative to 6-month animal). In addition, Ca^{2+} release was characterized in terms of the sum of the added Ca^{2+} and the endogenous Ca^{2+} of the mitochondrial preparation; the endogenous Ca^{2+} content was found to be unchanged with age. The decrements in rates of transport were not caused by altered rates of substrate oxidation and were inferred to refle decreased carrier protein content or activity. The buffering of extramitochondria free Ca^{2+} concentration by heart mitochondria was studied and found to be less tha complete at mitochondrial Ca^{2+} loads inferred to be physiological. No change was shown in senescence, in keeping with the essentially equal age-linked decrements in the activity of mitochondrial Ca^{2+} uptake and release.

(E) Regulation of salivary gland function

Studies continued to evaluate α-adrenergic mediation of K^+ efflux from the rat parotid gland *in vitro*. Specifically it was demonstrated that cells from aged rats, which were deficient in this secretory event compared to cells from younger rats, could release K^+ levels equivalent to that from young rats in response to the Ca^{2+} ionophore, A23187. This finding, coupled with earlier findings, suggests that parotid glands of aged rats had a deficit in mobilizing Ca^{2+} after α-adrenergic receptor stimulation.

Protein production and processing studies in rat submandibular gland cells *in vitro* were continued. Total protein production (CCl_3COOH precipitated dpm/μg DNA) was reduced (∿20%) in cells from older rats compared to younger rats, when evaluated with 3 separate radioactive precursors. Protein processing, evaluated by autofluorography and SDS-gel electrophoresis of newly synthesized proteins, in "older" cells showed distinct alterations from patterns seen with "young" cells.

(F) Studies on the oral physiological status of man during aging

Further studies of salivary gland function in BLSA subjects, utilizing the stimulated parotid gland, demonstrated specific changes in electrolyte secretion with increased age. While K^+ and Ca^{2+} secretion were constant in males and females over the adult life span, Na^+ release showed highly significant alterations. There was a linear decrease in sodium secretion (reflecting increased ductal Na^+ reabsorption) into stimulated parotid saliva with age. This decrease was greater in males than females.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF** **INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 AG 00043-09 LMA

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Regulation of Intermediary Metabolism

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	R. Hansford	Research Chemist	LMA, NIA
	B. Ashour	Visiting Fellow	LMA, NIA

COOPERATING UNITS (if any)

None

LAB/BRANCH
Gerontology Research Center, Laboratory of Molecular Aging

SECTION
Intermediary Metabolism Section

INSTITUTE AND LOCATION
NIA, NIH, Baltimore, Maryland 21224

TOTAL MANYEARS: 3.0	PROFESSIONAL: 2.0	OTHER: 1.0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

These studies seek to define and describe the molecular mechanisms whereby the major catabolic (*i.e.* energy-releasing) pathways of intermediary metabolism are controlled, and to investigate the ways in which these controls are altered in old-age. Such alterations are considered to underlie the decreased ability of senescent animals (including humans) to withstand environmental stresses (*e.g.* starvation, severe cold). Current investigations feature: (1) the control of pyruvate dehydrogenase and 2-oxoglutarate dehydrogenase activities by micromolar concentrations of Ca^{2+} ions; (2) the transport of Ca^{2+}-ions into and out of heart mitochondria and its relation to the homeostasis of cytosolic free Ca^{2+} concentrations; (3) the control of pyruvate dehydrogenase in skeletal muscle mitochondria and the effect of fatty acid and ketone oxidation; and (4) the impact of aging upon the transfer of cytosolic reducing equivalents into heart mitochondria by means of the malate/aspartate shuttle.

PHS-6040
(Rev. 2-81)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 AG 00048-08 LMA

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Ion Transport Mechanisms.

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	J. P. Froehlich	Medical Officer	LMA, NIA
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	A. S. Hobbs	Staff Fellow	LNC, NINDCDS
	R. L. Post	Professor of Physiology	Vanderbilt Univ.
	E. G. Lakatta	Chief, Cardiovascular Section	CPB, NIA
	G. Bhatanager	Staff Fellow, Cardiovascular Section	CPB, NIA

COOPERATING UNITS (if any) Laboratory of Neurochemistry, National Institute of Neurological and Communicative Disorders and Stroke, NIH; Department of Physiology, Vanderbilt University; Clinical Physiology Branch, NIA, NIH.

LAB/BRANCH
Gerontology Research Center, Laboratory of Molecular Aging

SECTION
Biophysics and Intermediary Metabolism Sections

INSTITUTE AND LOCATION
NIA, NIH, Baltimore, Maryland 21224

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
2.0	1.0	1.0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The mechanism of Ca^{2+} translocation in sarcoplasmic reticulum was investigated using fast kinetic methods. Results of these studies indicate that the translocation mechanism involves rapid transfer of Ca^{2+} from an external binding site to an occluded site prior to its release at the inner membrane surface. The kinetics of the phosphoenzyme intermediate reactions of the electric organ (Na,K)-ATPase were compared in the presence and absence of K^+. Results indicate the presence of K^+-activated acceleration of the phosphoenzyme interconversion reaction favoring a mechanism involving simultaneous occupation of Na^+ and K^+ transport sites. Examination of the initial turnover characteristics of the purified kidney (Na,K)-ATPase provides additional support for a simultaneous transport mechanism. The enzymatic partial reactions of the cardiac myofibrillar ATPase were examined with respect to Ca^{2+} sensitivity. Preliminary results indicate the presence of regulation of the steady state rate involving Ca^{2+}-activated release of reaction products.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 AG 00049-04 LMA

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Studies on the Oral Physiological Status of Man During Aging.

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	B. J. Baum	Dental Officer	LMA, NIA
OTHER:	L. Bodner	Visiting Fellow	LMA, NIA

COOPERATING UNITS (if any)

NONE

LAB/BRANCH
Gerontology Research Center, Laboratory of Molecular Aging

SECTION
Intermediary Metabolism Section

INSTITUTE AND LOCATION
NIA, NIH, Baltimore, Maryland 21224

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.2	0.2	0.0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

There has been little systematic investigation of tissues within the aging oral cavity. The purpose of this project is to assess the oral physiological status of participants in the Baltimore Longitudinal Study and thus provide baseline information which is lacking.

PHS-6040
(Rev. 2-81)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 AG 00050-04 LMA

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Regulation of Salivary Gland Function During Increased Age.

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	B. J. Baum	Dental Officer	LMA, NIA
OTHER:	L. Bodner	Visiting Fellow	LMA, NIA
	G. S. Roth	Research Chemist	CPB, NIA

COOPERATING UNITS (if any)

Endocrinology Section, Clinical Physiology, NIA.

LAB/BRANCH
Gerontology Research Center, Laboratory of Molecular Aging

SECTION
Intermediary Metabolism Section

INSTITUTE AND LOCATION
NIA, NIH, Baltimore, Maryland 21224

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.0	0.5	0.5

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Previous clinical observations have suggested that with increased age, decremental changes in salivary gland function occur. To study the mechanism of this alteration in animal models, salivary glands from young adult and aged male and female rats have been characterized biochemically and their regulation by neurotransmitters has been investigated.

PHS-6040
(Rev. 2-81)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 AG 00051-02 LMA

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Phosphate and Calcium Homeostasis, Relation to Senile Osteoporosis and Osteomalacia.

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

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	B. Bulos	Research Chemist	LMA, NIA
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	A. Jayakumar	Visiting Fellow (DOD 6/82)	LMA, NIA
	J. Rifkind	Research Chemist	LCMB, NIA
	D. Spector	Department of Medicine	Johns Hopkins U.
	E. Kraus	Department of Medicine	Johns Hopkins U.

COOPERATING UNITS (if any)
Department of Medicine, Johns Hopkins University, Baltimore, MD

LAB/BRANCH
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SECTION
Intermediary Metabolism Section

INSTITUTE AND LOCATION
NIA, NIH, Baltimore, MD 21224

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
8.6	4.1	4.5

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Osteoporosis is a leading cause of mortality and morbidity in aging women. The mechanisms of phosphate and calcium balance were studied as part of a major effort to understand the pathophysiological bases of senile osteoporosis and osteomalacia. Notable scientific achievements include the findings that (1) the active form of Vitamin D, 1,25-dihydroxy vitamin D$_3$, incubated *in vitro* with isolated kidney cells stimulates phosphate uptake, this increase being blocked by inhibitors of RNA and protein synthesis; (2) in vitamin D deficiency, the resultant secondary hyperparathyroidism causes blunted responses to PTH, at a site that generates cAMP and at a site distal to the activation of adenylate cyclase; (3) vitamin D$_3$ modifies membrane structure and function by liponomic regulation; (4) renal phosphate reabsorption is regulated by the serum phosphate level by a PTH-independent mechanism; and (5) PTH increases sodium-calcium exchange, a finding that may explain how the hormone acts to enhance calcium transport.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 AG 00052-02 LMA

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Pathophysiological and Hormonal Regulation of Membrane Transport Systems.

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	B. Sacktor	Chief, Lab. Molec. Aging	LMA, NIA
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	S. Hilden	Senior Staff Fellow	LMA, NIA
	L. Noronha-Blob	Senior Staff Fellow	LMA, NIA
	J. Kinsella	Staff Fellow	LMA, NIA
	M. Freiberg	Medical Officer	LMA, NIA
	U. Reiss	Visiting Associate	LMA, NIA
	S. El-Seifi	Visiting Fellow	LMA, NIA
	T. Uchida	Visiting Fellow	LMA, NIA
	G. Briefel	Department of Medicine	Johns Hopkins U.

COOPERATING UNITS (if any)
Johns Hopkins University, School of Medicine, Baltimore City Hospitals, Baltimore, MD 21224.

LAB/BRANCH
Gerontology Research Center, Laboratory of Molecular Aging

SECTION
Intermediary Metabolism Section

INSTITUTE AND LOCATION
NIA, NIH, Baltimore, MD 21224

TOTAL MANYEARS: 10.9	PROFESSIONAL: 8.4	OTHER: 2.5

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project studies the pathophysiological and hormonal regulation of membrane transport systems and the mechanisms by which age-dependent changes perturb physiological control systems and, thus, contributes to the failure to maintain homeostasis in the aged. Notable scientific achievements include the findings that: (1) glucocorticoids, but not mineralocorticoids, induce an increase in amiloride-sensitive sodium-proton exchange activity and a decrease in sodium-dependent phosphate uptake in renal membrane vesicles, findings consistent with the effects of glucocorticoids in stimulating acid secretion and causing phosphaturia; (2) in chronic uremia, the decreased phosphate transport is not attributable solely to an increased PTH level, uremic rats adapt normally to a low phosphorus diet, and the low phosphorus diet can reverse the phosphate transport decrement in uremic animals; (3) monoclonal antibodies reveal the presence of an antigenically distinct enzyme (maltase) in senescent animals; and (4) in established and primary kidney cell cultures, hormones and drugs that activate adenylate cyclase and protein kinase inhibit phosphate uptake.

Annual Report of the Laboratory of Neurosciences
National Institute on Aging

The Laboratory of Neurosciences at the National Institute on Aging was formed in 1978, and has embarked on a program of research on the central and peripheral nervous systems and muscle, in health, aging and disease. In 1982 the Laboratory will be divided into two sections, a clinical section on Brain Aging and Dementia, and a basic section on Cerebral Physiology and Metabolism. The Clinical Section is located at the Clinical Center in Bethesda and is directed by Dr. Neal Cutler. In October 1982, a 6-bed patient care unit will be established for an inpatient program to study patients with Alzheimer's and other dementias, as well as normal subjects. The basic section remains at the Gerontology Research Center in Baltimore, but will eventually move to Bethesda to provide a concerted program in the neurosciences.

This report summarizes the following projects: (A) Brain function in aging and dementia, (B) Cerebral metabolism, relation to brain function and aging, (C) Blood-brain barrier and central nervous system function, (D) Transport systems at the blood-brain barrier, (E) Drug pharmacokinetics, relation to the pharmacodynamics and senescence, (F) Pharmacology of central and peripheral catecholaminergic nervous systems, (G) Assessment of neurochemical markers in relation to age and behavior, (H) Synapse development, specificity and mechanism in culture, and (I) Function of peripheral nerve and muscle. Dr. N.R. Cutler is primarily responsible for project A, Dr. S.I. Rapoport and Dr. E. London for project B, Dr. Rapoport for project C, Dr. Q. Smith for project D, Dr. I. Kapetanovic for project E, Dr. M. Partanen for project F, Drs. E. London and S. Waller for project G, Drs. J. Thompson and B.A. Suarez-Isla for project H, and Drs. H. Levitan and M. Michel for project I.

A. Brain Function in Aging and Dementia.

In order to examine brain function during normal aging and in disease states, the major thrust of the clinical program has been to develop methods to measure cerebral metabolism by means of a new procedure recently introduced to the Clinical Center, namely positron emission tomography (PET). In the last 2 years, this laboratory has contributed to establishing the PET procedure and validating data obtained from it so that accurate and consistent measures of the regional cerebral metabolic rate for glucose ($rCMR_{glc}$) can be obtained under standardized and reproducible conditions.

18-F-2-deoxy-D-glucose was injected intravenously in 21 healthy men aged 21 - 83 years, as a positron-emitting analogue of glucose, to examine brain metabolism. $rCMR_{glc}$ was calculated from the data after PET scanning, which was performed under resting conditions when the subjects' eyes were closed and ears were plugged with cotton. It was found that $rCMR_{glc}$ did not change significantly ($p > 0.05$) with age in 27 right- and 27 left-sided brain regions, and that mean hemispheric glucose utilization also did not change with age in the 21 subjects. The age invariance of cerebral glucose utilization indicates that cerebral functional activity does not decline with age in man in the absence of disease, at least under resting conditions. Compensatory mechanisms must exist in the senescent human brain to counteract effects of many of the morphological and neurochemical changes which have been reported.

The subjects that were PET scanned were submitted to a complete medical, psychological and chemical workup. Data now are being evaluated to characterize the normal aging process. Psychological and psychomotor assessments indicated that reaction time was prolonged in these subjects with aging, that intelligence depending in part on learning did not decline but that factors in intelligence depending on memory and time-related operations declined with age. Studies with the Benton Visual Retention Test demonstrated age-related difficulty in encoding visual-spatial data and in sorting such data. Other findings were that pure tone and speech reception thresholds declined significantly with age, but that auditory parameters relating to middle ear function did not.

The study of normal aging will continue as more data are gathered. It is longitudinal in nature, and requires that the subjects return for evaluation every 2 - 5 years, depending on their age. The data gathered will be compared, furthermore, to data which we hope to gather in the next year on patients with Alzheimer's disease. The program on Alzheimer's disease will commence seriously when we get access to our inpatient care unit. An outpatient dementia clinic has been inaugurated, to identify patients for later study and to characterize Alzheimer's as compared to other dementias. Furthermore, A. Moore has commenced a support group for families of Alzheimer's patients, as a service and research program of the laboratory.

B. Cerebral Metabolism, Relation to Brain Function and Aging.

In an animal study parallel to the clinical study of brain metabolism and aging, it was demonstrated by E. London that the regional cerebral metabolic rate for glucose, as measured with ^{14}C-2-deoxy-D-glucose and autoradiography, increased between 1 and 3 months of age in awake Fischer-344 rats (when the rat brain continues to grow), declined between 3 and 12 months, but then remained unchanged during maturation and senescence (between 12 and 24, and 24 and 34 months of age). As in man, resting brain metabolism did not decline. We ascribed this lack of decline to compensatory responses of the senescent rat brain to age-related neurochemical and morphological losses.

In support of this hypothesis, H. Takei demonstrated that the cerebral metabolic rates for O_2 and for glucose, for the brain as a whole, as well as overall cerebral blood flow, did not change with age in awake Fischer-344 rats between 3 and 12, and 12 and 24 months.

The deoxy-D-glucose method was employed as a pharmacodynamic tool to examine where and to what extent the brain responds to drugs with specific actions. The muscarinic cholinergic agonist, oxotremorine, when administered to awake rats, produced a specific pattern of responses in brain regions, related in part to the presence of cholinergic receptors, whereas physostigmine, an inhibitor of acetylcholinesterase, produced a different response pattern. These data, relating to the cholinergic system, will eventually be applied to human studies, as losses of presynaptic cholinergic markers occur in normal aging and to a larger extent in Alzheimer's disease.

N. Shinowara related glucose utilization, as measured by the deoxy-D-glucose technique, to retinal morphology in albino Fischer-344 rats between 1 and 34 months of age. A progressive loss of photoreceptors was observed in the retina, and corresponded to a decline in retinal glucose utilization during aging. The findings clearly related cell loss in aging to deficits in metabolism and functional activity.

C. Blood-Brain Barrier and Central Nervous System Function.

Studies of the blood-brain barrier in health, disease and aging require quantitative measurements of cerebrovascular permeability and transport, and adequate pharmacokinetic theories to interpret drug distribution within the various brain compartments in relation to plasma concentrations and metabolism. Current techniques for measuring cerebrovascular permeability and transport are insensitive, semi-quantitative and can be influenced by changes in cerebral blood flow. My colleagues and I therefore elaborated and tested a quantitative procedure to measure blood-brain barrier permeability that can be used in conscious animals independent of cerebral blood flow and is at least 1000 times more sensitive than any other currently available technique.

With this procedure, we also demonstrated that the blood-brain barrier was not altered in rats following exposure to microwaves, although microwaves did modify cerebral blood flow in some brain regions. As humans are frequently exposed to microwaves, these studies should allay some of the fears concerning exposure which arose from previously reported, but probably erroneous findings of blood-brain barrier damage by microwaves.

A major problem in clinical psychopharmacology is that a central drug response often cannot be related directly to drug dosage or plasma concentration. In the elderly, furthermore, the high incidence of neurotoxic side effects may be caused by high concentrations of a drug, or altered receptor sensitivity to it. To consider these alternatives we established a general relation between cerebrovascular permeability and the octanol/water partition coefficient of a drug. We also formulated a multicompartmental pharmacokinetic model that incorporated the observed relation between permeability and partition coefficient, and that can be used to predict brain concentration of a psychoactive drug from the dosage and plasma concentration.

In 1972, we first demonstrated that the blood-brain barrier could be reversibly opened in animals by infusing a hypertonic solution of a water-soluble nonelectrolyte (e.g. urea, mannitol, arabinose) into the internal carotid artery. The effect later was shown to be caused by osmotic shrinkage of cerebrovascular endothelial cells, with consequent widening of interendothelial tight junctions. In the later years, we experimentally refined the osmotic method, and quantified changes of cerebrovascular permeability in relation to infusate concentration and infusion time, and demonstrated the reversibility of the osmotic effect. We showe that, when the barrier is opened osmotically, brain metabolism is transiently stimulated, brain edema is produced and metabolism is uncoupled transiently from cerebral blood flow. Thus, barrier integrity must be maintained continuously for normal cerebral function. In diseases which affect barrier integrity in man, changes in consciousness may be related to these central effects of barrier disruption.

On the basis of the animal studies, we initiated a clinical protocol with E.A. Neuwelt to apply the osmotic procedure in patients with metastatic brain tumors, so as to allow methotrexate and other anti-neoplastic drugs into the brain. We demonstrated with computerized assisted tomography that the blood-brain barrier can be opened reversibly in humans without producing apparent neurological changes. The clinical study is being continued to see whether the osmotic procedure will be efficacious for treating brain tumors.

Kernicterus commonly occurs in newborn and premature infants, but its cause and treatment remain controversial. Reduction of hyperbilirubinemia, on the basis of plasma concentrations of bilirubin, has not proven to be consistently effective in the clinic. We demonstrated, by combining hyperbilirubinemia in rats with osmotic barrier opening, that kernicterus can arise directly from barrier damage. This model should prove useful to examine the pathophysiology of kernicterus in the newborn.

D. Transport Systems at the Blood-Brain Barrier.

A controlled ionic composition of brain interstitial fluid is critical for normal neuronal and glial function, neurotransmission and synthetic processes. It was not known, however, to what extent ionic composition is regulated by the blood-brain barrier. Q. Smith demonstrated, clearly and for the first time, that chloride movement from plasma to brain in rats is carrier-mediated, saturable and subject to competitive interaction with other anions within the blood. Thus, in addition to acting as a permeability restriction to water-soluble drugs, the blood-brain barrier has clear regulatory properties which determine brain composition and thereby brain function. The extent of this regulation remains to be explored.

E. Drug Pharmacokinetics, Relation to Pharmacodynamics and Senescence.

The elderly respond differently to centrally-acting drugs than do mature adults. They are more susceptible to untoward sedation with benzodiazepines and to extrapyramidal symptoms with neuroleptics, drugs which are widely prescribed for them. Only limited information is available on the cause for the altered response.

I. Kapetanovic examined the pharmacokinetics of haloperidol in relation to age in Fischer-344 rats. This weak base, an antipsychotic agent which is metabolized mainly by N-dealkylation in the liver and is eliminated by metabolism, was found to have significantly higher plasma and brain concentrations in old rats as compared to young ones, following either a bolus injection or continuous chronic administration. The causes for this were a prolonged apparent plasma elimination half-life, reduced clearance, and higher brain/plasma distribution ratios in the elderly animals. These pharmacokinetic age-changes may account for increased toxicity of haloperidol in elderly man, and deserve to be examined in a clinical setting.

F. Pharmacology of Central and Peripheral Catecholaminergic Nervous Systems.

The Laboratory of Neurosciences previously demonstrated increased plasma concentrations of catecholamines in senescent Fischer-344 rats, but reduced responsivity of the cardiovascular and other systems to catecholamines. Increased concentrations may derive from paraganglia, extra-adrenal chromaffin tissue which are found in the para-aortic region of the rat, and are abundant in the fetus and at birth but degenerate postnatally. M. Partanen demonstrated that paraganglia tissues increase in quantity in senescent Fischer-344 rats, and contain, in the aged animals, large quantities of catecholamines that probably contribute to high plasma levels. Their later growth with sensescence may be an overall response of the sympathetic nervous system to reduced end organ sensitivity.

This hypothesis of increased activity of the sympathetic nervous system in the elderly is consistent with the demonstration by M. Partanen that glucose utilization, a measure of functional activity, was greater in the superior cervical ganglion of senescent than of young or mature Fischer-344 rats.

In response to stress, catecholamines are released and blood pressure is elevated. In man, cerebral metabolism and blood flow are said to be augmented by stress. These responses have been reported in rats as well. However, M. Ohata in our laboratory demonstrated that immobilization stress of awake mature rats did not increase cerebral blood flow and suggested that the stress effects reported previously in rats are erroneous. If blood-brain barrier integrity is maintained in stressed animals, circulating catecholamines probably are unable to enter the brain and stimulate brain metabolism and flow.

G. Assessment of Neurochemical Markers in Relation to Age and Behavior.

In related mouse strains, age-associated changes in several neurochemical markers such as neurotransmitter synthetic enzymes appear to be influenced by genetic variability. S. Waller and E. London examined three enzymes that are responsible for the synthesis of critical neurotransmitters, of which the function and concentration might be related to animal behavior. The enzymes were choline acetyltransferase (CAT), glutamic acid decarboxylase (GAD) and tyrosine hydroxylase (TH), responsible for the synthesis, respectively, of gamma-amino butyric acid, catecholamines and acetylcholine. The enzymes were measured in 4 brain regions of C57BL/6J and A/J mice strains, characterized by differences in activity and learning ability.

There was an approximately 30% increase in cerebellar TH activity in both strains between 4 and 24 months of age. There also were several age-associated alterations in enzyme activity that were strain-related. An example is GAD activity in the striatum between 4 and 24 months. It increased in C57BL/6J mice and decreased in A/J mice. In addition, normal mature C57BL/6J mice when compared to A/J mice, had higher TH and CAT activities in all four brain regions, higher cortical and cerebellar GAD activity, and lower hippocampal and striatal activity. The studies demonstrated that brain synthetic neurotransmitter enzymes are strain-related in mature animals, and that their pattern of change with aging depends on genotype. As these enzymes have also been measured in man, and shown to be affected in certain diseases (e.g. a reduced CAT activity in Alzheimer's disease), their characterization in relation to behavior and genotype should help to elucidate their role in cognition and behavior in man.

H. Synapse Development, Specificity and Mechanism in Culture.

J. Thompson demonstrated that synapse formation, synapse termination, synapse specificity and neurotransmission can be studied using neurons and muscle cells in tissue culture. He detected functional synapses by inserting microelectrodes into muscle cells, and recorded miniature end plate potentials in these cells. He demonstrated that neurons from retina or chick spinal cord form long-lived synapses with muscle cells in culture. Each type of neuron, therefore, possesses a synapse-competent state during its development, when it can form abundant synapses with muscle cells in culture. Dr. Thompson's results suggest a mechanism of synapse specificity that is based on stabilization of correct synapses which is coupled with a synaptogenic period during development for each type of neuron. Dr. Thompson's studies also demonstrate that synapse formation and retention can be studied in a controlled fashion in tissue culture. His findings may be critical for our interpretation of neuronal cell death in the aging nervous system.

Specifically, Dr. Thompson showed that rat retinal neurons formed synapses only between the 18th day of embryonic development and day 7 after birth, with a maximum number formed from pups 1 day old. Neurons from the chick embryo spinal cord formed synapses after 2 days, the maximum number with 4-day neurons. The capacity to form synapses decreased with age, and was observed after 51 hr but not after 24 hr of co-culture with neurons from 18-day embryo spinal cord. Thus, spinal cord neurons do not completely lose their ability to form synapses with muscle cells. All neurons tested show decreased ability to form synapses as they aged during development. The neurons also lose their ability to form synapses when maturing *in vitro* in a manner and time course which parallels the loss of their ability to form synapses during *in ovo* maturation. Neurite extension by neurons *in vitro* also changed with development. There was a statistically significant age-related decrease in the percentage and average length of neurites formed in 24-hr cultures of chick retina and spinal cord neurons between 6- and 16-days of embryonic age. These results imply that maximal rates of neurite extension and synaptogenesis occur concurrently during development and suggest that neurite extension is critical to synaptogenesis.

In tissue culture studies, neuroblastoma cells lines have become important *in vitro* models for neuronal systems. Dr. Thompson demonstrated, contrary to current opinion, that three commercial neuroblastoma lines are not homogeneous, and that more than one cell type is presented in them. This means that studies with them may have to be re-evaluated.

I. Function of Peripheral Nerve and Muscle.

The blood-nerve barrier consists of the perineurium, which surrounds the nerve, and the endoneural capillaries which are comparable to continuous capillaries in the central nervous system. Little is known about how these barrier sites affect nerve growth and function. With electron microscopic tracer techniques, N. Shinowara and M.E. Michel characterized the perineurium of the frog sciatic nerve as a system of concentric layers of flattened cells interspersed by collagen fibers and connected by tight junctions. They showed that the cells had numerous pits and vesicles, and demonstrate with colloidal and ionic lanthanum that the vesicles were connected to the cell surfaces and never formed transcellular channels. They are examining the contribution of these vesicles to perineural function.

We examined the relation of metabolism to fatigue in single twitch muscle fibers of the frog, a correlative study which had been done only in whole muscles in which some fibers can fatigue faster than others and measured metabolite concentrations are averaged over a heterogeneous fiber population. Muscle fatigue generally is thought to be caused by depletion of energy reserves. However, we demonstrated that tetanized single fibers lost their ability to contract when energy reserves, in the form of adenosinetriphosphate (ATP), were maintained at high levels. These energy reserves were not sequestered, because they could be depleted by caffeine administration. On the basis of these findings and measured lactate concentrations, we proposed a new hypothesis to account for muscle fatigue, namely that H^+, as lactic acid, accumulates in muscle during repetitive stimulation to interfere with excitation-contraction coupling and prevent contraction.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 AG 00126-03 LNS

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Brain Function in Aging and Dementia

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	N.R. Cutler	Section Chief	LNS NIA
	S.I. Rapoport	Chief	LNS NIA
	R. Duara	Medical Staff Fellow	LNS NIA
	M. Schwartz	Medical Staff Fellow	LNS NIA
	E.A. Robertson-Tchabo	Psychologist (IPA)	LNS NIA
	R.A. Margolin	Medical Staff Fellow	LNS NIA
	C.L. Grady	Psychologist	LNS NIA
	E.D. London	Pharmacologist	LNS NIA
	A.M. Moore	Social Worker	LNS NIA
Others:	J. Rapoport	Chief	MBB NIMH
	R.M. Kessler	Staff Physician	CC NM
	J.M. De Leo	Computer Systems Analyst	CSL DCRT
	J.W. Renfrew	Psychologist	LNS NIA
	B.J. Koziarz	Psychologist	LNS NIA
	T. Colburn	Electronics Engineer	RSB NIMH

COOPERATING UNITS (if any)

LAB/BRANCH
Laboratory of Neurosciences

SECTION

INSTITUTE AND LOCATION
NIA, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: 9.3	PROFESSIONAL: 7.3	OTHER: 2

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The Section on Brain Aging and Dementia, located in Bethesda, is studying brain function and metabolism in healthy men at different ages, and in patients with Alzheimer's disease and autism. Brain glucose utilization in specific regions was measured by positron emission tomography (PET) scanning and 18-Fluorodeoxyglucose. Statistically significant declines in glucose utilization did not occur in men between 21 and 83 years, indicating that oxidative metabolism remains normal in the healthy elderly, under resting conditions and in the absence of disease. Psychometric evaluation showed age-related decline in memory but not in parameters of crystallized intelligence (verbal ability). Reaction time increased with age. Overall motor activity, as measured with a patient activity monitor, fell with age. An outpatient dementia clinic was established for evaluation and screening of subjects with various types of dementia.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 AG 00125-04 LNS

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Cerebral Metabolism, Relation to Brain Function and Aging

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	E.D. London	Pharmacologist	LNS	NIA
	A.S. Kimes	NIH Research Fellow	LNS	NIA
	M. Ohata	Visiting Fellow	LNS	NIA
	M. Dam	Visiting Fellow	LNS	NIA
	H. Takei	Visiting Fellow	LNS	NIA
	P. Helen	Visiting Fellow	LNS	NIA
	S.I. Rapoport	Chief	LNS	NIA
Others:	H.W.Holloway	Biologist	LNS	NIA
	W.R. Fredericks	Biologist	LNS	NIA
	N. L. Shinowara	Sr Staff Fellow	LNS	NIA
	P.R. Mahone	Biologist	LNS	NIA
	A.E. Ellis	Biol Lab Tech	LNS	NIA
	D. Dow-Edwards	Staff Fellow	LNS	NIA

COOPERATING UNITS (if any)

LAB/BRANCH
Gerontology Research Center, Laboratory of Neurosciences

SECTION

INSTITUTE AND LOCATION
NIA, NIH, Baltimore, MD 21224

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
6.7	4.1	2.6

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

1) Cerebral metabolism was studied in relation to age and drug responses in unanesthetized rats. Regional cerebral glucose utilization (rCMRglc) as measured with ^{14}C-2-deoxy-D-glucose, increased during development in Fischer-344 rats, but remained constant during senescence. 2) Cerebral metabolic rates for O_2 and glucose did not decline significantly between 3 and 24 months of age. 3) In adult rats, central muscarinic stimulation with oxotremorine increased rCMRglc in areas involved in motor and cognitive function. Blockade of acetylcholine degradation with physostigmine increased rCMRglc in central optic pathways and the nucleus of the trigeminal nerve. 4) An age effect in the rCMRglc response to oxotremorine was observed during the second year of life in rats. 5) GABA agonists generally decreased rCMRglc, but produced a relative increase in the dentato-rubro-thalamic pathway. 6) There is a clear relation between loss of retinal photoreceptors during aging of the albino rat, and the decline in glucose utilization. 7) Incorporation of ^{14}C-palmitate in the rat brain can be employed to quantitatively examine regional function.

PHS-6040
(Rev. 2-81)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 AG 00120-05 LNS

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Blood-Brain Barrier and Central Nervous System Function

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	S.I. Rapoport	Chief	LNS	NIA
	M. Ohata	Visiting Fellow	LNS	NIA
	E.D. London	Pharmacologist	LNS	NIA
	Z. Ziylan	Visiting Fellow	LNS	NIA
	Q. Smith	Staff Fellow	LNS	NIA
	P. Robinson	Visiting Fellow	LNS	NIA
Others:	K.D. Pettigrew	Math Statistician	DBE	NIMH
	R. Fitzhugh	Res. Physicist	LB	NINCDS
	W.R. Fredericks	Biologist	LNS	NIA
	S. Gruenau	Psychologist	NAMRI*	
	E. Neuwelt	Neurosurgeon	Univ. of Oregon Medical School	
	R.L. Levine	Staff Scientist	LB	NHLBI

COOPERATING UNITS (if any) Theoretical Statistics and Mathematics Branch, DBD, NIMH
Laboratory of Biophysics, NINCDS
*Naval Medical Research Institute, Bethesda
University of Oregon Medical School, Portand, OR

LAB/BRANCH
Gerontology Research Center, Laboratory of Neurosciences

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NIA, NIH, Baltimore, Maryland 21224

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
3.7	2.7	1.0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A method was developed to measure cerebrovascular permeability to water-soluble as well as lipid-soluble drugs. Pharmacokinetic principles for the central nervous system were established that should make it possible to calculate brain concentrations of drugs from measured plasma concentration curves and peripheral metabolic rates. Cerebrovascular integrity was not changed in rats following microwave exposure, although such exposure altered regional cerebral blood flow. Opening of the blood-brain barrier, by osmotic means or by hypertension, uncoupled cerebral blood flow from metabolism, caused brain edema, and stimulated brain glucose utilization. Osmotic opening of the blood-brain barrier was employed in rats to allow protein-bound bilirubin into the brain, as an experimental model of clinical kernicterus. It also has been used in man for allowing methotrexate into the brain, in the treatment of metastatic brain tumors.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 AG 00129-02 LNS

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Transport Systems at the Blood-Brain Barrier

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	Q.R. Smith	Staff Fellow	LNS	NIA
Others:	S.I. Rapoport	Chief	LNS	NIA
	Y. Takasato	Visiting Fellow	LNS	NIA

COOPERATING UNITS (if any)

LAB/BRANCH
Gerontology Research Center, Laboratory of Neurosciences

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INSTITUTE AND LOCATION
NIA, NIH, Baltimore, Maryland 21224

TOTAL MANYEARS: 1.9	PROFESSIONAL: 1.9	OTHER: 0

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☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Ionic homeostasis in the rat brain was examined by measuring chloride (Cl) transport at the blood-brain barrier under different experimental conditions. Plasma [Cl] of pentobarbital-anesthetized rats was varied acutely between 114 mM and 16 mM by means of peritoneal dialysis. Thereafter, constant Cl concentrations were maintained by bilateral nephrectomy. The blood to brain transfer constant (k) of Cl was determined in different brain regions by measuring brain radioactivity at 30 min after the radioisotope, Cl^{36}, was injected intravenously. The transfer constant varied 2-fold in the range of Cl concentrations examined, and could be described by saturation (Michaelis-Menton) kinetics. Monovalent anions competitively inhibited Cl movement into the brain. The concentration dependence of Cl uptake, and inhibition by monovalent anions, indicate that Cl crosses the blood-brain barrier by a carrier mediated mechanism.

PHS-6040
(Rev. 2-81)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF** **INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 AG 00128-02 LNS

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Drug Pharmacokinetics, Relation to Pharmacodynamics and Senescence

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	I.M. Kapetanovic	Senior Staff Fellow	LNS	NIA
Others:	S.I. Rapoport	Chief	LNS	NIA
	D.J. Sweeney	Chemist	LNS	NIA

COOPERATING UNITS (if any)

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LAB/BRANCH
Gerontology Research Center, Laboratory of Neurosciences

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INSTITUTE AND LOCATION
NIA, NIH, Baltimore, Maryland 21224

TOTAL MANYEARS: 1.7	PROFESSIONAL: .7	OTHER: 1

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☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Effects of age on pharmacokinetics of central nervous system drugs were studied. Biodisposition of haloperidol and phenobarbital was examined in male, Fischer-344 rats of four different age groups, 3-4, 11-12, 23-24, and 32-34 months. Drugs were administered intraperitoneally, either as a bolus or continuously from implanted osmotic minimpumps. Plasma and brain concentrations were determined for these drugs, after extraction, by gas chromatographic analysis with a nitrogen selective detector. Similar age-related alterations in pharmacokinetic profiles of these two drugs were observed although the drugs have different pharmacotherapeutic, physicochemical and pharmacokinetic properties. Significantly higher plasma and brain concentrations of both drugs were found in the older as compared to younger rats, due to a decreased apparent plasma clearance following a bolus and during continuous administration. Plasma concentrations were not directly predictive of brain concentrations, because the brain/plasma concentration ratio of the drugs did not remain constant during aging. These studies are a first step to understanding of altered clinical responsivity to drugs in the elderly.

PHS-6040
(Rev. 2-81)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF** **INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 AG-00122-05 LNS

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Pharmacology of Central and Peripheral Catecholaminergic Nervous Systems

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	M. Partanen	Visiting Fellow	LNS NIA
	M. Ohata	Visiting Fellow	LNS NIA
	S.I. Rapoport	Chief	LNS NIA
Others:	E.D. London	Pharmacologist	LNS NIA
	I. Linnoila	Sr. Staff Fellow	LP NCI
	A. Hervonen	Professor	Univ of Tampere
	W.R. Fredericks	Biologist	LNS NIA
	U. Sundaram	Student	LNS NIA
	C.C. Chiueh	Senior Staff Fellow	LNS NIA

COOPERATING UNITS (if any)

University of Tampere, Finland
Laboratory of Pathology, National Institutes of Health

LAB/BRANCH
Gerontology Research Center, Laboratory of Neurosciences

SECTION

INSTITUTE AND LOCATION
NIA, NIH, Baltimore, Maryland 21224

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.5	1.5	0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

1. Immobilization stress does not increase regional cerebral blood flow in conscious rats, indicating that cerebral metabolism, to which blood flow is coupled, is insensitive to increased circulating catecholamines. The blood-brain barrier may contribute to this insensitivity.

2. Glucose utilization (GU) tends to increase in sympathetic ganglia between 12 and 24 months of age in the Fischer-344 rat. The increase is statistically significant in the superior cervical ganglion, and may be related to increased circulating norepinephrine.

3. Paraganglia, which contain catecholamines and are extra-adrenal chromaffin tissue, degenerate after birth in the rat but reappear between 24 and 33-months of age, and contain high concentrations of catecholamines.

4. Catecholamine fluorescence mapped from single neuron perikarya decreased with age in certain peripheral sympathetic ganglia as well as in certain brain regions which contain catecholamine-containing neurons.

PHS-6040
(Rev. 2-81)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 AG 00127-02 LNS

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Assessment of Neurochemical Markers in Relation to Age and Behavior

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	Edythe D. London	Pharmacologist	LNS	NIA
	Steven B. Waller	Staff Fellow	LNS	NIA
Others:	Stanley I. Rapoport	Chief	LNS	NIA
	Donald K. Ingram	Staff Fellow	LBS	NIA

COOPERATING UNITS (if any)

Laboratory of Behavioral Sciences

LAB/BRANCH
Gerontology Research Center, Laboratory of Neurosciences

SECTION

INSTITUTE AND LOCATION
NIA, NIH, Baltimore, Maryland 21224

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.3	1.2	.1

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Age effects on neurochemical markers and the correlation between brain neurochemical markers and motor performance were tested in C57BL/6J and A/J mice. Motor performance was altered by age, and age effects varied with genetic strain. Age-associated decrements in performance were correlated with regional changes in cholinergic, GABAergic, and catecholaminergic neurochemical markers. Activities of choline acetyltransferase (CAT), glutamic acid decarboxylase (GAD), and tyrosine hydroxylase (TH) were assayed in four brain regions after animals were evaluated in a battery of psychomotor tests. Significant correlations between enzyme activity and motor performance occurred most frequently in the youngest (4-mo) and oldest (24-mo) groups. Examination of age effects on the cholinergic markers, CAT activity and muscarinic binding in C57BL/6J mice revealed regional increases in CAT activity that were associated with increases in Vmax, and no changes in Km. In the cerebral cortex and striatum, these increases in Vmax were associated with decreases in the muscarinic binding sites.

PHS-6040
(Rev. 2-81)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 AG 00123-04 LNS

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Synapse Development, Specificity and Mechanism in Culture

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	J.M. Thompson	Sr Staff Fellow	LNS	NIA
	B.A. Suarez-Isla	Visiting Fellow	LNS	NIA
Others:	S.I. Rapoport	Chief	LNS	NIA
	C.L. Makino	Biochem Lab Tech	LNS	NIA

COOPERATING UNITS (if any)

LAB/BRANCH
Gerontology Research Center, Laboratory of Neurosciences

SECTION

INSTITUTE AND LOCATION
NIA, NIH, Baltimore, Maryland 21224

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
3.0	3.0	0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords) Synapse formation, synapse specificity and neurotransmission were studied using neurons and muscle cells in culture. Synapses were detected and investigated by electrophysiological recording. Neurons from chick and rat retina and chick spinal cord form synapses with muscle cells. Each type of neuron possesses a synapse-competent state in its development during which it can abundantly form synapses with muscle cells in culture. In addition, developmental periods for maximal neurite extension correlate with the developmental periods for synaptogenesis. These results suggest a mechanism of synapse specificity based on a synaptogenic period during development for each type of neuron. Synapse specificity can also be based on differences in synapse stabilization. Inappropriate synapses, such as rat or chick retina neurons on muscle cells, are transient; while appropriate synapses, such as spinal cord on muscle, are stabilized. Neuroblastoma cell lines can be used as in vitro model systems for neural function. Three neuroblastoma cell lines have been characterized for their morphology, neurochemistry and ability to form synapses. Neurotransmitter release can be studied in an in vitro perfusion system. Acetylcholine release increases during development and maturation of chick retina synapses. Dopamine release from rat striatal slices does not change during aging.

PHS-6040
(Rev. 2-81)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 AG 00121-05 LNS

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Function of Peripheral Nerve and Muscle

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	M.E. Michel	Staff Fellow	LNS	NIA
	H.L. Levitan	Physiologist (IPA)	LNS	NIA
	P. Ask	Visiting Fellow	LNS	NIA
	S. Odman	Visiting Fellow	LNS	NIA
	P. Robinson	Visiting Fellow	LNS	NIA
	S.I. Rapoport	Chief	LNS	NIA
Others:	N.L. Shinowara	Senior Staff Fellow	LNS	NIA
	K.C. Wadhwani	Student Investigator	LNS	NIA
	J.V. Passonneau	Chief	LNS	NINCDS
	V. Nassar-Gentina	Research Scientist	Univ	of Santiago
	R.E. Taylor	Research Physiologist	LNS	NINCDS
	A. Weerasuriya	Visiting Associate	LNS	NIA

COOPERATING UNITS (if any)
Lab of Neurochemistry and Lab of Biophysics, NINCDS
Dept of Physiol, Univ of Santiago, Chile

LAB/BRANCH
Gerontology Research Center, Laboratory of Neurosciences

SECTION

INSTITUTE AND LOCATION
NIA, NIH, Baltimore, Maryland 21224

TOTAL MANYEARS: 4.2	PROFESSIONAL: 4.2	OTHER: 0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A. The perineurium of frog sciatic nerve, which regulates nerve function, contains concentric cell layers that act as a diffusion barrier because of the presence of tight junctions. The cells have vesicles which take up extracellular lanthanum but do not form complete transcellular channels. Perineurial permeability is low to ions and water-soluble nonelectrolytes, but high to lipid soluble nonelectrolytes. There is evidence of active ion transport. The hydrostatic pressure in the nerve is positive and reflects the role of the perineurium as an osmotically active membrane. Nerve capillaries form part of a blood-nerve barrier.

B. Fatigue of single frog muscle fibers appears as a decline in tension output during prolonged tetanic stimulation. The concentration of adenosinetriphosphate (ATP) (an energy source for contraction) remained normal in fatigued fibers. Furthermore, ATP was not available for contraction, because it could be consumed during caffeine-induced contractures. We suggest that H^+, as lactic acid, accumulates in fatigued fibers and interferes with excitation-contraction coupling.

NIA Annual Report
October 1, 1981 through September 30, 1982
Gerontology Research Center
Laboratory of Cellular and Molecular Biology

The Laboratory of Cellular and Molecular Biology brings together various research projects that are related through a common interest in genetic information transfer, the biological aging process, and molecular mechanisms of physiological phenomena. The Section on Inorganic Biochemistry is concerned with fundamental studies at the molecular level of biological macromolecules involved in genetic information transfer. Age changes are investigated in systems involving these molecules, and particular emphasis is placed on the beneficial as well as harmful effects of metal ions that interact with these molecules. The Section on Macromolecules is concerned with the interaction of cell surfaces and receptors with synthetic substances, particularly macromolecules. These studies are aimed at the elucidation of cellular processes and the design of better drugs to interfere with such processes, especially those involved in diseases of the elderly. The Section on Cellular Aging and Genetics has been concerned with cell replication and repair of DNA damage, but the activities of this section are on a small scale, in comparison with activities before the departure of the former section head. Plans to build a new section which would utilize the new recombinant-DNA technology for studies of biological aging had to be abandoned because of the loss of positions.

The discovery of a new form of DNA, the Z-conformation in polymers or oligomers of d(G-C) has created much excitement among molecular biologists, especially since antibody reactions have indicated that the Z-conformation is present in significant amounts in the DNA of cell nuclei. It is believed that conformational transitions such as B-DNA to Z-DNA are useful in genetic regulation. The B → Z transition can be induced by metal complexes. We have discovered that, in the presence of such a complex, the B → Z transition is only the first step in a series of conformational changes, and that the Z form is converted into another structure, identifiable by its CD spectrum, which resembles that of A-DNA. It may well be A-DNA, but we call it X-DNA, because we cannot be sure at this time that it is identical with any previously discovered form of DNA. X-DNA is then converted into the familiar ψ-DNA, the highly associated anisotropic structure whose dependence on metal ions we have studied extensively in the past. Equilibria between the four DNA conformers are affected by concentrations of poly(dGdC), of the metal complex, temperature and reaction time. The reaction sequence $B \rightleftarrows Z \rightleftarrows X \rightleftarrows \psi$ is fully reversible by treatment with strong electrolyte. It is possible to manipulate reaction conditions so that any of the DNA forms can be stabilized, i.e., the reaction can be stopped at any intermediate, e.g., Z or X. But it is also possible to observe all these transitions between the four structures as three consecutive reactions. Clearly, any consideration of the B → Z transition must also take into account further equilibria that involve X and ψ-DNA.

If the transition between DNA conformers are important in genetic regulation, it is of great interest to determine whether these transitions affect the ability of DNA to act as template for RNA synthesis. Such studies require an experimental design that can differentiate between the effects of the structural transitions and the agents that bring about the transition. We found that the reagent for the B → Z transition, $[Co(NH_3)_6]^{3+}$, activates RNA polymerase activity when poly(dAdT) or calf thymus DNA are templates, but inhibits RNA synthesis when poly(dGdC) is template. Thus the transition reagent inhibits only when a template capable of conversion to the Z-form is present; the other templates actually cause the reagent to activate RNA polymerase. Thus it appears that the Z-structure is a poor template for RNA synthesis. We do not quite understand, however, why inhibition occurs with poly(dGdC) template at reagent concentrations that are too low to cause a change to the Z-form, as detected by CD. Perhaps the enzyme can recognize B → Z transitions that occur in only part of the DNA molecule, and which cannot be detected by CD. However, the enzyme has some capability of converting the Z to the B-structure, and this capability increases with enzyme concentration.

^{27}Al-NMR in aqueous solution has been pioneered in our laboratory to elucidat structures of complexes that may be relevant to Alzheimer's disease. Phosphate, carboxyl and hydroxyl ligands have been employed to examine the effects of ligand, coordination state, ligand field symmetry and exchange rate on the Al(III) signal. Slow exchange phenomena have permitted the determination of the number and types of complexes of Al(III) with these ligands, their exchange rates and their reactio

^{31}P-NMR studies have been used to elucidate the reaction of Al(III) with DNA and chromatin. The complex of Al(III) with DNA at pH 5 has a spectrum that can be resolved into two peaks, one corresponding to the peak due to complexed DNA and the other representing a new peak due to complexing. Heating produces a spectrum containing only the Al(III) complex peak. We have previously shown that this Al(III) complex contains Al crosslinks between the DNA strands, and we have obtain new evidence for such crosslinks from the disappearance of a 13.6 ppm peak in the ^{1}H-NMR spectrum that arises from the G-C hydrogen bond. Evidently the Al has displaced this H-bond. The crosslinks are stable at pH 5, but increasing pH brings about renaturation of the DNA that had been previously crosslinked by aluminum. When Al(III) reacts with either "oligonucleosomal" chromatin (consisting of 7-10 nucleosomes) or mononucleosomes derived from calf thymus, chicken erythrocyte or rat liver nuclei, a peak again appears downfield from the uncomplexed DNA peak. Thus the Al seems to bind to chromatin in the same fashion, i.e. by crosslinking DNA strands, as in naked DNA. When the pH is raised, another peak appears which presumably is due to $Al(OH)^{2+}$ bound to DNA phosphates. The downfield-shifted peak are not observed in a chromatin preparation from normal human brain obtained from autopsy, but the NMR spectrum of chromatin derived from the brain of patients who died from Alzheimer's disease looks just like the spectrum of chromatin that had been reacted with aluminum.

We have found a very sensitive probe for DNA accessibility in chromatin, in the form of Cu^{2+} ions. These do not normally bind to chromatin; the chromatin structure appears to prevent the Cu^{2+} from getting to the DNA. However, if H-1 histone is removed, or if Mg^{2+} ions are added at high concentration, or if histones are partially acetylated, the Cu^{2+} then binds to chromatin DNA. Cu^{2+} apparently cannot pentrate the chromatin structure when the H-1 is intact, but if it is removed, or loosened, as by the immobilization of amino groups through acetylation, the Cu^{2+} can get through.

Studies with RNA polymerase have shown that the presence or absence of a poly(dAdT) template does not affect the conformation of ATP substrate bound with Mn^{2+} ions to the enzyme. This bonding confirms the postulate of Mildvan, based on previous NMR studies, that the Mn^{2+} itself is responsible for orienting the nucleotide in the proper conformation for fitting the double helix.

Studies have been initiated on the determination of the effects of metal ions on aging in tissue culture. The objective is to find how the permeability of cells to ions changes with age and what effects the metal ions that penetrate the cell have on genetic information transfer within the cell. We have developed an accurate, reproducible atomic absorption technique for measuring zinc levels in cultured cells from human fetal lung fibroblasts (IMR-90). When challenged with sublethal amounts of zinc, late passage cells accumulate twice as much zinc as early passage cells. The increased rate of uptake of metal ions occurs consistently through a 30-hour time period.

Sister chromatid exchanges (SCEs) are known to be sensitive indicators of DNA damage and possibly repair. $Pt(NH_3)_2Cl_2$ is a known mutagen which binds to DNA in a highly specific manner. We have been examining the ability of this compound to induce SCE in cultured fibroblasts with increasing passage level. Initial findings indicate that Pt induces approximately 50% fewer SCE in later passage cultures. In addition, pretreating the cultures with minute amounts of platinum before adding the full SCE-inducing dose diminishes SCE levels in both early and late passage cultures by 45-50%. This finding may indicate a conditioning mechanism utilized by the cells in response to mutagenic substances.

A study of age-related changes in cell metabolism of animal models in vivo was initiated using ^{31}P NMR. A custom-made surface coil NMR probe capable of detecting ^{31}P signals from metabolites selectively from the brain or kidney was required for this study. The probe was built using the machine shop facilities at the GRC and is being tested at present. Being a non-invasive technique, NMR holds great promise for the continuous monitoring of metabolism in the animals.

Beta-adrenergic antagonists are extensively used to treat hypertension, cardiac arrhythmias, and angina pectoris. Numerous studies with these drugs show that the drug's effects are due to a blockade of receptors for adrenergic hormones, which are located on the surface of cells. Many potent beta-adrenergic antagonists contain a pharmacophore, $Aryl-O-CH_2-CHOH-NH-$, attached to a secondary or tertiary allyl group. New beta-adrenergic antagonists containing several of such complete or partial pharmacophores of this type were prepared and studied. These compounds had the general structure: $R_2N-CH(CH_3)-CH_2-[O-CH_2-CH-(CH_3)]-2-8NR_2$, where R is either H- or $Aryl-O-CH_2-CHOH-CH_2-$ group. Synthesis was achieved by reaction of aryl glycidyl ethers with Jeffamines^R, which are primary diamines used in the manufacture of plastics. The following aryl groups were used: 2-allyphenyl, 4-(2-methoxyethyl)phenyl, 1-naphthyl, and 4-methoxyphenyl. The first three correspond to moieties of the established drugs alprenolol, metoprolol, and propranolol, respectively. The affinities of these compounds for beta-adrenergic receptors of rat heart and lung were estimated by measuring their ability to compete with the specific binding of $(-)[^3H]$dihydroalprenolol. Compounds containing one pharmacophore bound to the receptors with affinities comparable to those of the parent drugs and the blockade of receptors could be dissociated by successive washes as easily as were those of the parent drugs. Compounds containing two or three pharmacophores had somewhat lower affinities for receptors, but the resulting blockade was persistent even after successive washing. These findings suggest that drugs with several pharmacophores may crosslink several receptors, a phenomenon that can lead to a persistent blocking of receptors. Treatment by antihypertensive agents, a group of drugs to which beta-adrenergic blockers belong, is required for about 31% of the elderly. The above described results on beta-adrenergic blockers suggest that irreversibly acting drugs may gain a role in geriatric pharmacology. The development of drugs that would need to be administered only weekly would be of advantage since the total amount of drug used would decrease and senescent organisms are known not to handle xenobiotics well.

Lipid-soluble vitamins, in addition to their obvious nutritional values, have further beneficial effects. Unfortunately, to obtain a significant measure of these additional effects, doses that already elicit toxicity are required. Thus retinoids, which are derivatives of vitamin A, have been shown to reduce the incidence of lesions in epithelium induced by carcinogens. Work done in this progra focuses on lessening the toxic effects of retinoids through transforming them to a water soluble form by complexation with solubilizing agents. Cyclodextrins, compounds obtainable in the processing of starch, were used as starting materials in the preparation of solubilizing agents. Substitution by alkyl groups in cyclodextrins yielded compounds which enabled the preparation of stable aqueous isotonic solutions that contained up to milligram amounts of retinoids per milliliter Presently, we found that 2,6-di-O-methyl-beta-cyclodextrin (cyclohepta-2,6-di-O-methylamylose) considerably accelerated and increased the dissolution of all-trans retinoic acid. 2,6-di-O-methyl-beta-cyclodextrin also affected the toxicity of retinoic acid in mice in a manner depending on the way of administration: (a) when 2,6-di-O-methyl-beta-cyclodextrin was administered simultaneously with retinoic acid, the toxic effects of the latter were considerably increased and set in rapid without the typical symptoms of hypervitaminosis A; (b) when 2,6-di-O-methyl-beta-cyclodextrin was administered alone, after the hypervitaminosis A had been established, the survival rate was improved.

The spectrin-actin cytoskeleton is anchored to the erythrocyte membrane by interaction with integral membrane proteins and is thought to play a major role in regulating the shape and deformability of the cell as well as mobility and function in other parts of the membrane. We have developed a technique to attach spin labels specifically to sulfhydryls on spectrin and to follow conformational changes on the cytoskeleton by monitoring alterations in the ESR spectra of these spin labels. MgATP, which has previously been shown to play a role in regulating the shape of erythrocyte ghosts, has also been shown to produce a dramatic change in the ESR spectrum of these spin labels. We have shown that the effect of MgATP on the ESR and the shape of the ghost does not involve hydrolysis of the ATP. Thus non-hydrolyzable analogues of ATP like AMPPNP and APPCH$_2$P produce similar effects. We in fact find effects on the ESR spectra and the shape of the erythrocyte ghosts with ATP alone and Mg alone. There must therefore be cation sites and polyvalent anion sites on the cytoskeleton which produce conformational changes which enable shape changes to take place. Our results suggest that the MgATP interacts with the ATP site with a greater affinity than ATP alone and therefore produces greater effects. Zinc produces effects on the ESR spectrum similar to, but even greater than, MgATP. Zinc, perhaps by binding to the same cation sites as Mg, produces conformational changes similar to those of MgATP and thereby stabilize the membrane structure. The conformation of spectrin and thereby the functional properties of the membrane seems to be carefully regulated by the temperature and the binding of a number of different species present in the cell.

We previously found that cholesterol can be oxidized to cholesten-3-one by cholesterol oxidase in intact erythrocytes but that the rate is much slower than in liposomes. We have now found that even resealed ghosts react 10 times faster than intact ghosts, and leaky ghosts react 80 times faster than intact cells with approximately the same rate as liposomes prepared for erythrocyte lipids. We can produce rather large changes in the rate of this reaction with various drugs such as chlorpromazine and propranolol, by altering the ratio of cholesterol to phospholipid, and by treating the membrane with phospholipase. We have been able to detec large changes in rate even under conditions when no change in membrane fluidity is detected by ESR or fluorescent probes. These studies indicate that the oxidation by cholesterol oxidase is extremely sensitive to even minor changes in membrane structure. The sensitivity of this reaction suggests that it should be sensitive to changes which take place during aging. We have in fact found an increase in the velocity for intact cells and resealed ghosts during cellular aging.

We have found that the cholesterol/phospholipid ratio of adipocyte ghosts increases with age. This result is consistent with other results on various membranes which indicate that the cholesterol content of membranes increases with age. Higher cholesterol content generally produces a decrease in membrane fluidity particularly at physiological temperatures. However, we find that even though the older ghost membranes are less fluid below 10°C, they are actually more fluid at physiological temperatures. These adipocyte ghosts contain both the plasma membrane and the endoplasmic reticulum. We have shown that the plasma membrane has a considerably higher cholesterol/phospholipid ratio and is less fluid than the endoplasmic reticulum. We are trying to determine whether the apparent contradiction between the change in lipid composition and the change in fluidity with age can be explained by the presence of two different membrane fractions where the relative amounts of both as well as their lipid composition may change with age.

We have found that even at 210°K there is a rearrangement of methemoglobin resulting in the formation of reversible complexes with the distal histidine. These complexes have ESR and Mossbauer spectra similar but not identical to that of hemichromes. However, unlike other hemichrome structures, they are immediately reversible at elevated temperatures. These changes reflect conformational equilibria in the ligand pocket of the heme. Mossbauer studies with carbonmonoxy hemoglobin indicate that similar conformational equilibria in this ferrous hemoglobin perturb the orientation of CO bound to hemoglobin at low temperature. These results actually suggest that the most stable conformation for the heme pocket may involve interference of the distal histidine with binding of ligands. The heme pocket may thus play a major role in controlling the binding of ligands to hemoglobin.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 AG 00044-09 LCMB

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Effect of Metals and Proteins on Nucleic Acids, Information Transfer and Aging

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	G. L. Eichhorn	Chief, LCMB	LCMB NIA	
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	S. J. Karlik	Visiting Fellow	LCMB NIA	(DOD 9-30-82)
	R. P. Pillai	Visiting Associate	LCMB NIA	(EOD 6-27-82)

COOPERATING UNITS (if any)
Laboratory of Molecular Biology, NIAMDD; Department of Biophysics, Johns Hopkins University

LAB/BRANCH
Laboratory of Cellular and Molecular Biology

SECTION
Section on Inorganic Biochemistry

INSTITUTE AND LOCATION
NIA, NIH, Baltimore, Maryland 21224

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
7.0	6.0	1.0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project focuses on the interaction of molecules concerned with genetic information transfer. A primary objective is to determine under what conditions metal ions are essential for information transfer, and under what conditions they produce errors in the information and may thus contribute to biological aging. Topics of interest are: (1) the effects of metal ions on the structure of nucleic acids, nucleoproteins and chromatin; (2) age-related changes in chromatin structure; (3) aging of ribosomes; (4) the mechanism of involvement of aluminum in Alzheimer's disease; (5) crosslinking of nucleic acid strands by metal ions; (6) the effects of metal ions on RNA polymerase; (7) metal ions and cellular aging.

PHS-6040
(Rev. 2-81)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 AG 00088-10 LCMB

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Mechanisms of Cellular Aging

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

Robert E. Monticone	Biologist	LCMB NIA
Gunther L. Eichhorn	Chief, LCMB	LCMB NIA

COOPERATING UNITS (if any)

LAB/BRANCH
Laboratory of Cellular and Molecular Biology

SECTION

INSTITUTE AND LOCATION
NIA, NIH, Baltimore, Maryland 21224

TOTAL MANYEARS: 2	PROFESSIONAL: 2	OTHER: 0

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☒ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Studies are carried out to determine the effects of metal ions on cellular aging. The object is to determine how the permeability of the cells to ions changes with age and what effects the metal ions that penetrate the cell have on genetic information transfer within the cell.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE
PROJECT NUMBER (Do NOT use this space)

U.S. DEPARTMENT OF
HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NOTICE OF
INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 AG 00046-12 LCMB

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)
Potential Drugs for Diseases Prominent in Senescence

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	J. Pitha	Chief, MCS	LCMB NIA	
OTHERS:	J. Kusiak	Special Expert	LCMB NIA	
	T. Czajkowska	Visiting Associate	LCMB NIA	(EOD 06/27/82)
	G. Heja	Visiting Fellow	LCMB NIA	(EOD 04/19/82)
	J. Milecki	Visiting Fellow	LCMB NIA	(DOD 11/30/81)
	M. Stern	Visiting Fellow	LCMB NIA	(EOD 09/01/81)
	L. Szente	Visiting Fellow	LCMB NIA	(DOD 05/07/82)

COOPERATING UNITS (if any)
Key Pharmaceuticals, Miami, FL; University of Florida, Gainesville, FL; George Washington University, Washington, D.C.; UMAB Foundation, University of Maryland, Baltimore, MD.

LAB/BRANCH
Laboratory of Cellular and Molecular Biology

SECTION
Macromolecular Chemistry Section

INSTITUTE AND LOCATION
NIA, NIH, Baltimore, Maryland 21224

TOTAL MANYEARS: 5.5	PROFESSIONAL: 4.5	OTHER: 1.0

CHECK APPROPRIATE BOX(ES)
☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Two groups of drugs which are heavily used by the elderly have been subjected to molecular manipulations in order to learn how their pharmacological profiles can be improved. In the group of beta-adrenergic blockers it has been established that introduction of several pharmacophores into one molecule results in a considerably protracted blockade. In the field of fat soluble vitamins it has been established that cyclodextrin derivatives can be used for rescue from hypervitaminosis A.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 AG 00047-12 LCMB

PERIOD COVERED

October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Structure-Function Relationships in Hemoglobin and Erythrocytes

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	J. M. Rifkind	Research Chemist	LCMB NIA
OTHER:	J. G. Mohanty	Visiting Fellow	LCMB NIA
	T. Suda	Visiting Fellow	LCMB NIA

COOPERATING UNITS (if any)

Johns Hopkins University

LAB/BRANCH

Laboratory of Cellular and Molecular Biology

SECTION

Section on Inorganic Biochemistry

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
3.6	2.6	1.0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☒ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The purpose of this project is to study the mechanisms involved in regulating the binding of oxygen to hemoglobin and the transport of oxygen to the tissues. The project also focuses on ways in which these functions are impaired and change with age. We have therefore studied the mechanisms involved in the oxidation of hemoglobin. Oxidation affects oxygen transport because it produces nonfunctional hemoglobin, which no longer binds oxygen. These studies have been extended to include an investigation of the stability of the entire erythrocyte and the erythrocyte membrane as well as other structure function relationships in membranes.

PHS-6040
(Rev. 2-81)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 AG 00010-9 CPB

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)
Noninvasive Assessment of the Left Ventricle in Normal Man

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	J. L. Fleg	Staff Cardiologist		CPB, NIA
	D. N. Das	Staff Fellow	DOD 6/28/82	CPB, NIA
	E. G. Lakatta	Chief, Cardiovascular Section		CPB, NIA
Other:	None			

COOPERATING UNITS (if any)

LAB/BRANCH
Gerontology Research Center, Clinical Physiology Branch

SECTION
Cardiovascular Section

INSTITUTE AND LOCATION
NIA, NIH, Baltimore, Maryland 21224

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.8	0.03	0.05

CHECK APPROPRIATE BOX(ES)
☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

To determine the chest x-ray findings attributable to normal aging, we evaluated standard postero-anterior chest x-rays taken at least 10 years apart in 67 healthy men initially ages 23-76 years. The mean aortia knob diameter increased from 3.4 ± 0.6 cm to 3.8 ± 0.5 cm, and mean cardiothoracic ratio (CTR) increased from .41 ± .04 to .43 ± .04. Pulmonary abnormalities on initial chest x-ray consisted mainly of hyperinflation (27%) and increased markings (19%), both of which doubled in prevalence during follow-up. Chronic obstructive lung disease was suggested in 15% of the initial films and 21% of the final films despite the absence of clinical or spirometric abnormalities.

To assess the effect of age on cardiac performance during exercise, we have via a collaborative effort with Johns Hopkins Division of Cardiology two-dimensional echocardiography and more recently radionuclide angiocardiography in our BLS population. In addition, exercise thallium scintigraphy has been performed on nearly 400 individuals to characterize the prevalence and distribution of coronary artery disease.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 AG 00029-05 CPB

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Efficacy of Digitalis in Patients with Stable Congestive Heart Failure and in Normal Subjects

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	J. L. Fleg	Staff Cardiologist	CPB, NIA
	E. G. Lakatta	Chief, Cardiovascular Section	CPB, NIA
Other:	None		

COOPERATING UNITS (if any)
S. H. Gottlieb, Division of Cardiology, Baltimore City Hospitals, Baltimore, Maryland

LAB/BRANCH
Gerontology Research Center, Clinical Physiology Branch

SECTION
Cardiovascular Section

INSTITUTE AND LOCATION
NIA, NIH, Baltimore, Maryland 21224

TOTAL MANYEARS: 0.05	PROFESSIONAL: 0.05	OTHER:

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

These studies comprised two parts. (1) A double-blind crossover study of digitalis in patients with stable congestive heart failure (CHF) and sinus rhythm showed that digitalis could be discontinued for three months without adverse clinical effect and only a 3 per cent increase in resting heart size and 10 per cent decline in velocity of fiber shortening. The new dimension to this aspect of the study is that long-term follow-up (11-33 mo) of these patients has verified our favorable initial experience in discontinuing digitalis. (2) We have recently compared the effects of a digitalis intravenous bolus in healthy young and elderly men, employing systolic time intervals as a monitor of the inotropic effect and have found no age effect.

PHS-6040
(Rev. 2-81)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 AG 00030-04 CPB

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Altered Contractile and Mechanical Properties in Senescent Model Tissues: Rat Heart; Dog Aortas

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	H. A. Spurgeon	Physiologist	CPB, NIA
	E. G. Lakatta	Chief, Cardiovascular Section	CPB, NIA
	E. S. Beard	Chemist	CPB, NIA
Other:	None		

COOPERATING UNITS (if any)

F. C. P. Yin, Division of Cardiology, Department of Medicine, Johns Hopkins Medical Institutions

LAB/BRANCH
Gerontology Research Center, Clinical Physiology Branch

SECTION
Cardiovascular Section

INSTITUTE AND LOCATION
NIA, NIH, Baltimore, Maryland 21224

TOTAL MANYEARS: 0.4	PROFESSIONAL: 0.4	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Increased dynamic stiffness across the frequency range from 35 to 0.5 Hz in maximally activated strips of aorta obtained from senescent beagles as compared to adults was demonstrated. These changes accompany changes in intrinsic impedance measured in the same animals prior to sacrifice. Dynamic stiffness measured during a cardiac contraction in rat cardiac muscle has been shown to be dependent on the degree of activation produced by adjustment of bathing calcium concentration, and implies that stiffness measured thusly is in part directly related to the activation process.

Combined into Project Z01 AG 00036-02 CPB

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 AG 00032-04 CPB

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Contractile, Biochemical and Electrical Catecholamine Responses in Hyperthyroid Heart

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	E. G. Lakatta	Chief, Cardiovascular Section	CPB, NIA
	H. A. Spurgeon	Physiologist	CPB, NIA
	E. S. Beard	Chemist	CPB, NIA
Other:	None		

COOPERATING UNITS (if any)

J. Y. Wei, Beth Israel Hospital, Boston, MA

LAB/BRANCH
Gerontology Research Center, Clinical Physiology Branch

SECTION
Cardiovascular Section

INSTITUTE AND LOCATION
NIA, NIH, Baltimore, Maryland 21224

TOTAL MANYEARS: 1.0	PROFESSIONAL: 1.0	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Changes that occur within the cardiac cell in response to β-adrenergic stimulation result in a dual effect on the mammalian cardiac contraction: a potentiating effect, manifest as an enhancement of twitch force, and a relaxant effect, evidenced by a decrease in the time to peak force and an enhanced rate of relaxation. Since these two manifestations of the relaxant effect occur concomitantly, it is not known whether they are governed by one or more than one mechanism. One approach toward an understanding of this would be to selectively block one of the relaxant effects of β-adrenergic stimulation. We have observed in the hyperthyroid heart that the effect of catecholamines to shorten time peak force does not occur, but that the enhancement of the rate of relaxation of the terminal twitch is preserved. Thus these two manifestations of the relaxant effect occur via different mechanisms. It can be hypothesized that the shortening of time to peak force results from enhanced calcium accumulation rate of sarcoplasmic reticulum, which is blunted in the hyperthyroid model, while the effect later in the twitch may be attentuable to catecholamine induced phosphorylation of troponin resulting in less calcium affinity.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 AG 00033-04 CPB

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Ambulatory Electrocardiography and Blood Pressure Measurement in Normal Man

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	J. L. Fleg	Staff Cardiologist		CPB, NIA
Other:	D. N. Das	Staff Fellow	DOD 6/28/82	CPB, NIA
	E. G. Lakatta	Chief, Cardiovascular Section		CPB, NIA

COOPERATING UNITS (if any)

LAB/BRANCH
Gerontology Research Center, Clinical Physiology Branch

SECTION
Cardiovascular Section

INSTITUTE AND LOCATION
NIA, NIH, Baltimore, Maryland 21224

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.0	0.4	0.6

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Initial ambulatory electrocardiographic work from this laboratory has characterized the normal heart rhythm patterns in healthy elderly subjects. We have extended these efforts to include younger men and women (ages 25-60). In addition, we have added a new dimension - 24 hour ambulatory blood pressure (BP) recording - simultaneous with the ambulatory ECG recording, in normal subjects as well as hypertensives and those with congestive heart failure.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 AG 00035-03 CPB

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Fluctuations in the Intensity of Light Scattered through Diastolic Cardiac Muscle

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	E. G. Lakatta	Chief, Cardiovascular Section	CPB, NIA
	K. P. Brin	Staff Fellow DOD 6/27/82	CPB, NIA
	A. A. Kort	Clinical Associate	CPB, NIA
	G. M. Bhatnagar	IPA Research Scientist	CPB, NIA

Other: None

COOPERATING UNITS (if any)

M. Stern, Division of Cardiology, Department of Medicine, Johns Hopkins Medical Institutions

LAB/BRANCH
Gerontology Research Center, Clinical Physiology Branch

SECTION
Cardiovascular Section

INSTITUTE AND LOCATION
NIA, NIH, Baltimore, Maryland 21224

TOTAL MANYEARS: 1.8	PROFESSIONAL: 1.7	OTHER: .1

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

We have discovered that scattered light intensity fluctuations (SLIF) are present in isolated rat ventricular muscle even under conditions formerly considered to be quiescent. Subsequent experiments indicated that SLIF are highly dependent on calcium loading of the cell and could be reversibly terminated (1) by maintaining constant calcium concentration in the myofilament space in skinned fibers or (2) in intact fibers by caffeine. These results were interpreted to indicate that cellular myoplasmic calcium concentration oscillates in diastole, producing motion of the myofilaments, which modulates the laser beam resulting in SLIF. This myofilament motion which is asynchronous within a cell, and among cells, results in a small degree of diastolic force or "tone" in the muscle. We have also examined the relationship of the SLIF frequency and force development in response to subsequent excitation and have found very high correlations. Thus, the oscillatory calcium pool monitored by SLIF appears to be intimately related to excitation-contraction coupling in muscle. More recent experiments have demonstrated SLIF in atrial, ventricular and conduction tissues in a range of mammalian species including man and indicate the universality of this phenomenon in excitable cardiac tissues. GRC/CPB-77

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 AG 00036-02 CPB

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Interaction of Age and Physical Conditioning Variables on Myocardial Contractility

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	H. A. Spurgeon	Physiologist	CPB, NIA
	E. G. Lakatta	Chief, Cardiovascular Section	CPB, NIA
	E. S. Beard	Chemist	CPB, NIA
Other:	M. F. Steinbach	Biologist	CPB, NIA

COOPERATING UNITS (if any)
F. C. P. Yin, Division of Cardiology, Department of Medicine, Johns Hopkins Medical Institutions

LAB/BRANCH
Gerontology Research Center, Clinical Physiology Branch

SECTION
Cardiovascular Section

INSTITUTE AND LOCATION
NIA, NIH, Baltimore, Maryland 21224

TOTAL MANYEARS: 2.0	PROFESSIONAL: 0.5	OTHER: 1.5

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

As previously reported, physical conditioning appears to be effective in modifying myocardial performance in the senescent heart. Because of the obvious importance of this area, we have undertaken to development of exercise models. In addition to the wheel exercise as previously reported, other programs varying age, duration, and intensity and type of exercise have been added to the model development program. Specifically the addition of life long daily swimming in both male and female rats has been developed.

PHS-6040
(Rev. 2-81)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 AG 00037-2 CPB

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Adaptation of Cardiac Muscle to Chronic Volume Overload is Altered by Age

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	G. D. Walford	Clinical and Research Fellow, PHS	CPB, NIA
	E. G. Lakatta	Chief, Cardiovascular Section	CPB, NIA
	E. S. Beard	Chemist	CPB, NIA

Other: None

COOPERATING UNITS (if any)

LAB/BRANCH
Gerontology Research Center, Clinical Physiology Branch

SECTION
Cardiovascular Section

INSTITUTE AND LOCATION
NIA, NIH, Baltimore, Maryland 21224

TOTAL MANYEARS: 1.2	PROFESSIONAL: 1.0	OTHER: .2

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

When the heart is faced with an increased work load on a chronic basis, cardiac hypertrophy results. With aging, certain changes occur in the cardiac cell which may alter the response to a chronically imposed work load, i.e., there may be an interaction of the adaptation to this stress and aging. The present study was undertaken to determine whether such an interaction could be demonstrated. The elucidation and understanding of such an interaction is central to the well known observation that cardiac pathologic conditions that impose an increased work load become more severe with aging or the passage of time.

PHS-6040
(Rev. 2-81)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 AG 00038-01 CPB

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Evaluation of Peripheral Blood Flow in Normal Man by Plethysmography

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	D. N. Das	Staff Fellow	DOD 6/28/82	CPB, NIA
	J. L. Fleg	Staff Cardiologist		CPB, NIA
	E. G. Lakatta	Chief, Cardiovascular Section		CPB, NIA
Other:	None			

COOPERATING UNITS (if any)

LAB/BRANCH
Gerontology Research Center, Clinical Physiology Branch

SECTION
Cardiovascular Section

INSTITUTE AND LOCATION
NIA, NIH, Baltimore, Maryland 21224

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.50	.30	.20

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Although the incidence of degenerative changes in the blood vessels is well known to increase with advancing age, quantitative data on the peripheral blood flow due to the aging process are lacking. Venous occlusion plethysmography has been shown to be the most accurate and reproducible method to measure the peripheral blood flow. We used this method to evaluate peripheral blood flow in the subjects of the Baltimore Longitudinal Study of Aging with ages ranging from 20 to 83 years. The study was designed to evaluate the effect of age on peripheral blood flow by venous occulsion plethysmography during rest and in response to removal of arterial occlusion and thermal stress.

PHS-6040
(Rev. 2-81)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 AG 00039-01 CPB

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)
Long-term Prognosis of Asymptomatic Men with Complete Right Bundle Branch Block

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	J. L. Fleg	Staff Cardiologist	CPB, NIA
	D. N. Das	Staff Fellow DOD 6/28/82	CPB, NIA
	E. G. Lakatta	Chief, Cardiovascular Section	CPB, NIA
Other:	None		

COOPERATING UNITS (if any)

LAB/BRANCH
Gerontology Research Center, Clinical Physiology Branch

SECTION
Cardiovascular Section

INSTITUTE AND LOCATION
NIA, NIH, Baltimore, Maryland 21224

TOTAL MANYEARS: 0.3	PROFESSIONAL: 0.3	OTHER:

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The long-term cardiac prognosis of 24 clinically healthy men with complete right bundle branch block (RBBB), identified from the 1140 men constituting the BLS population, was assessed over a follow-up period averaging 8.4 years. When compared with a control group matched for age at which RBBB appeared, men with RBBB showed no difference in the prevalence of antecedent coronary risk factors or obstructive lung disease. Their incidence of angina pectoris, myocardial infarction, valvular heart disease, cardiomegaly, congestive heart failure, advanced heart block, or cardiac death did not differ from that of the control group over the observation period. Furthermore, at latest follow-up maximal aerobic exercise tolerance and chronotropic response to maximal exercise were not impaired in men with RBBB relative to controls. However, axis deviation leftward of -30° was present in 46% of RBBB men but only 15% of controls by latest follow-up. Although a PR interval prolongation greater than 40 msec developed in only 6% of control subjects over the observation period, such prolongation occurred in 29% of men with RBBB. These results support the concept that RBBB in these asymptomatic men is a manifestation of a primary abnormality of the cardiac conduction system but has no demonstrable adverse effect.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF** **INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 AG 00040-01 CPB

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Thermal Sensitivity of Resting Force in Rat Cardiac Muscle: Relationship to Twitch Characteristics.

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	E. G. Lakatta	Chief, Cardiovascular Section	CPB, NIA
	H. A. Spurgeon	Physiologist	CPB, NIA
	G. Ruano-Arroyo	Guest Scientist	CPB, NIA

Other: None

COOPERATING UNITS (if any)

LAB/BRANCH
Gerontology Research Center, Clinical Physiology Branch

SECTION
Cardiovascular Section

INSTITUTE AND LOCATION
NIA, NIH, Baltimore, Maryland 21224

TOTAL MANYEARS: 1.0	PROFESSIONAL: 1.0	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The contractile performance of isolated myocardium is critically dependent on temperature. From 32 to 16°C, both diastolic and systolic force as well as contraction duration increase exponentially. Diastolic force approached thermal insensitivity when bathing medium calcium was removed. Diastolic force predicts by simple linear functions the entire profile of the ensuing contraction, including systolic force, rates of force development, and contraction duration. These findings are suggestive of an underlying contractile process common to both the diastolic and systolic states of the muscle.

GRC/CPB-82

PHS-6040
(Rev. 2-81)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 AG 00221-01 CPB

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Sodium-Calcium Dependence of Resting Force in Rat Cardiac Muscle

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	E. G. Lakatta	Chief, Cardiovascular Section	CPB, NIA
	G. D. Walford	Clinical Associate	CPB, NIA
Other:	None		

COOPERATING UNITS (if any)
G. Gerstenblith, Division of Cardiology, Department of Medicine, Johns Hopkins Medical Institutions

LAB/BRANCH
Gerontology Research Center, Clinical Physiology Branch

SECTION
Cardiovascular Section

INSTITUTE AND LOCATION
NIA, NIH, Baltimore, Maryland 21224

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.0	1.0	

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

It has been recently demonstrated that an increase in perfusate calcium concentration within the millimolar range results in an increase in "resting" force in unstimulated rat cardiac muscle. To determine whether this apparent calcium influx occurs via a passive "leak" of calcium down its electrochemical gradient or might be mediated, in part at least, via a Na/Ca exchange was the focus of the present study. In isometric rat right ventricular papillary muscles equilibrated at 29°C, stimulation was stopped and sodium, potassium or calcium concentrations were varied in various combinations in the presence and absence of ouabain and caffeine. The resulting apparent change in cellular calcium was monitored by measurements of resting force. The apparent increase in cellular calcium following a step increase in perfusate calcium was highly dependent on conditions that effect intracellular sodium, the results are best explained by a sarcolemmal Na/Ca exchange mechanism. Furthermore, the results suggest that this mechanism can operate in the direction to load the cell with calcium even in the unstimulated state and in part modulates the calcium-dependent portion of resting force observed in the rat.

PHS-6040
(Rev. 2-81)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)

U.S. DEPARTMENT OF
HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
**NOTICE OF
INTRAMURAL RESEARCH PROJECT**

PROJECT NUMBER

Z01 AG 00222-01 CPB

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Altered Mechanical Properties in Myocardium from Rats Subjected to Chronic Food Deprivation

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	H. A. Spurgeon	Physiologist	CPB, NIA
	E. G. Lakatta	Chief, Cardiovascular Section	CPB, NIA
	E. S. Beard	Chemist	CPB, NIA
	D. Ingram	Staff Fellow	LBS, NIA

Other: None

COOPERATING UNITS (if any)

F. C. P. Yin, Division of Cardiology, Department of Medicine, Johns Hopkins Medical Institutions, Baltimore, Maryland

LAB/BRANCH
Gerontology Research Center, Clinical Physiology Branch

SECTION
Cardiovascular Section

INSTITUTE AND LOCATION
NIA, NIH, Baltimore, Maryland 21224

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.6	0.4	0.2

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Prolongation of life-span by restricted feeding of laboratory animals is an often repeated and well accepted finding. Little data exists relative to the physiological modification of cardiac performance associated with food restriction. Animals in the present series have been maintained on life-long food restriction by ad-libidum feeding on an every other day sequence (EOD) and are compared with cohort matched controls. Preliminary data shows a premature age deficit and appears to indicate that senescent age changes in myocardial performance can be made to occur out of phase with chronological age by food restriction, i.e., occur at an earlier age.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF** **INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 AG 00223-01 CPB

PERIOD COVERED

October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Effect of Age on the Components of Atrioventricular Conduction in Normal Man

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	D. N. Das	Staff Fellow	DOD 6/28/82	CPB, NIA
Other:	J. L. Fleg	Staff Cardiologist		CPB, NIA
	E. G. Lakatta	Chief, Cardiovascular Section		CPB, NIA

COOPERATING UNITS (if any)

LAB/BRANCH
Gerontology Research Center, Clinical Physiology Branch

SECTION
Cardiovascular Section

INSTITUTE AND LOCATION
NIA, NIH, Baltimore, Maryland 21224

TOTAL MANYEARS: 0.4	PROFESSIONAL: 0.3	OTHER: 0.1

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

We have utilized a signal averaging, high resolution ECG to record His bundle potentials from the body surface of 80 normal Baltimore Longitudinal Study (BLS) volunteers ages 21 to 79. By allowing measurement of conduction time both proximal and distal to the bundle of His, this technique should enhance our understanding of the age-related changes in the cardiac conduction system.

PHS-6040
(Rev. 2-81)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 AG 00224-01 CPB

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Cardiac Myofibrillar ATPase Activity Across a Broad Age Range

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	G. M. Bhatnagar	IPA Research Scientist	CPB, NIA
	E. S. Beard	Chemist	CPB, NIA
	G. D. Walford	Clinical Associate	CPB, NIA
	E. G. Lakatta	Chief, Cardiovascular Section	CPB, NIA
Other:	None		

COOPERATING UNITS (if any)

LAB/BRANCH
Gerontology Research Center, Clinical Physiology Branch

SECTION
Cardiovascular Section

INSTITUTE AND LOCATION
NIA, NIH, Baltimore, Maryland 21224

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1	1	0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Myofibrillar ATPase activity and the force-pCa relationship, were measured in rat cardiac preparations across a broad age range. Between 2 and 6 months, maximum ATPase activity in detergent treated myofibrils decreased approximately twofold (0.166 ± 0.01 vs 0.078 ± 0.02 micromolar Pi/min/mg/protein, P less than .001), but did not change with further aging (12 or 24 mo). Calcium-dependent force in thin "Triton skinned" papillary muscles were not age-related. ATPase activity and force exhibited identical calcium sensitivity from the submicromolar to micromolar range. No age differences in these parameters were observed. In the intact muscles prior to skinning, neither twitch force nor the rate of force production were age-related; however, time to peak force, half relaxation time, increased progressively, changing by approximately 30% across the age span (P less than .001). Since the decline in ATPase activity occurred over the maturational period only, and did not change with further aging, while the twitch duration changed progressively with age, it is concluded that the twitch prolongation of the senescent myocardium cannot be directly related to the age-related decline in myofibrillar ATPase activity.

PHS-6040
(Rev. 2-81)

ENDOCRINOLOGY SECTION

Annual Report Summary for October 1, 1981 to September 30, 1982

The Endocrinology Section is engaged in a variety of projects that are directed to the goal of better understanding the biochemical and physiologic bases of age-related alterations of hormone and neurotransmitter secretion and action. The studies involve intact human subjects, animal models, tissue and cell culture techniques, and cell-free systems.

Age-related alterations of β-adrenergic mediated lipolysis in the rat have been under study by our group for a number of years. Although we have confirmed and extended the suspected decrease of β-adrenergic hormone responsiveness that occurs with age in rat fat cells, difficulties of using this system as a model of aging have emerged. In the first place, the results using our GRC rats have proved to be very different from those of our colleagues at the University of Texas who are using the Fisher 344 strain. Our animals showed less of an age decrement (± 50% vs 90%) for the Texas group and did so only at very advanced age, while the Fisher rats showed a progressive change from early maturity through mid-life. This qualitative and quantitative difference demands further elucidation, since--with the large variance and lesser effect of age in our animals--it would be difficult or impossible for us to pursue the mechanism of the age effect. We considered two possibilities: 1) a strain (i.e., genetic) difference; and 2) an environmental factor. Since the rats in the two studies were fed different diets, we considered and had reason from the results of other studies in the literature to believe that this latter possibility of diet was a significant factor. Because of financial constraints we have not ourselves been able to implement a study using the Fisher rat.

In exploring the issue of diet the following facts have emerged. First, both the amount of fat in the diet and the type of fat (degree of unsaturation) are important variable for the hormone-sensitive lipolytic response. Second, the dietary fat has a profound effect on the lipid composition of cell membranes and the latter in turn controls the activity of numerous cell membrane enzymes, including the hormone-sensitive adenylate cyclase system. Furthermore, even within the same animal the effect of altered dietary fat is not the same in every tissue. Thus, while little or no effect of a high unsaturated fat diet is seen on fat cell membranes, the membranes of liver cells are grossly affected and exhibit increased hormone-responsiveness to both catecholamines (epinephrine) and polypeptide hormones (glucagon). In addition, in our rats, a relatively high fat diet, but one which is comparable to that used by others with the Fisher 344, is strikingly inhibitory to lipolytic responsiveness. This inhibition seems to involve the lipolysis inhibitor adenosine.

It is obvious from these complex results that age is only one of many variables in the control of lipolysis and that a great deal of work remains to be done in this area if we are to begin to understand the interrelationships and mechanim(s) of the age-effects. On the other hand, the fat cell system is still one of the best defined, single-cell systems available for a biochemical dissection of age-related alteration of hormone action.

In a separate but related project, we have been able to extend work first published by us over 5 years ago when we reported that in the liver of old rats a doubling of epinephrine-sensitive adenylate cyclase activity was apparent. Some of our evidence at that time suggested that the mechanism seemed to involve some alteration of the liver cell membrane, but we wished as a first step to determine if β-adrenergic receptors were involved. Did these increase in number as cyclase activity increased? If not, our notion that an intramembrane even was involved seemed even more reasonable. However, despite a huge effort we could not quantitate β-receptors in adult/senescent livers. The reasons were largely technical. However, we persisted and finally discovered that a new β-antagonist is a suitable compound for this purpose. Remarkably, our early data indicate that b-receptors increase several-fold more than does epinephrine-sensitive adenylate cyclase, i.e., receptors increase about five-fold during aging. To our knowledge, no such increase of β receptors has ever been seen under any other physiologic or pathophysiologic condition, including aging. This striking phenomenon should be a useful proble for future aging studies.

In other studies we have focused on steroid hormones and neurotransmitters of the adrenergic, cholinergic, dopaminergic and opioid types.

Attempts have been made to elucidate the mechanisms of previously demonstrated reduced responsiveness to glucocorticoids and estrogens in a variety of aged cells and tissues including adipocytes, uterus, skin, pituitary cells, testes (Leydig cells) and heart. Altered responses include control of nutrient transport and metabolism, regulation of hormone production and release, and modulation of various physiological functions including wound healing and muscle contraction.

In some cases loss of steroid receptors during aging appears to be at least partially responsible for impaired responsiveness. In others, alterations in post receptor components and events may play a role (e.g., reduced sensitivity of the aged adipocyte membrane glucose transport system, possibly related to physiochemical changes including altered fluidity properties).

Beyond these levels of action we have observed age related reductions in sensitivity to the permissive effects of glucocorticoid hormones. Such phenomena may partially explain diminished responsiveness of aged Leydig cells to gonadotropin and cardiac muscle to adrenergic agents. Interestingly, glucocorticoids may exert permissive effects in these and other systems through modulation of Ca^{++} mobilization, a process now appearing to be frequently impaired during aging (see below).

Certain responses to neurotransmitters are altered during aging in heart, the central nervous system, and rat parotid gland cells. These cells provide an interesting model system in which to distinguish selective age changes in adrenergic and cholinergic regulation. While cholinergic mechanisms remain functionally intact over virtually the entire lifespan, various α-adrenergic responses, like some of the β-adrenergic systems mentioned, show selective patterns of age related change. For example, α-adrenergic amylase release remains constant throughout life; α-adrenergic K^+ release diminishes between 3 and 12 months; while α-adrenergic stimulated glucose oxidation diminishes between 12 and 24 months. The latter two responses are mediated through α_1-adrenergic receptors which are not lost during aging. Instead age changes occur in phospholipid turnover and Ca^{++} transport which mediate these responses. In fact if sufficient Ca^{++} can be made to enter aged cells by using the ionophore A23187, age differences are abolished. This observation is strongly reminiscent of β-adrenergic myocardial contraction, also Ca^{++} dependent, in which similar elimination of age related impairment can be effected by increasing medium Ca^{++} concentration.

Dopaminergic and opiatergic mechanisms in various brain regions also exhibit age dependent alterations. Responses include thermoregulation and modulation of nociception for the opioids and stereotypy and stimulation of adenylate cyclase for dopamine. Studies have attempted to identify the particular receptor subtypes which are lost during aging, and these include the μ-opiate receptors and the D_1, D_2, and D_3 dopaminergic receptors. Receptor biosynthetic rates also appear to decline with age. This may be analagous to the situation for adipocte and fibroblast glucocorticoid receptors and cardiac β-adrenergic receptors. We have also attempted to elucidate the control mechanisms governing CNS neurotransmitter receptors including modulation by age changes in membrane fluidity and selective neuroendocrine regulation of receptor concentration. In addition we have retarded age related dopamine receptor loss by dietary restriction of rats.

The effect of age on the metabolic clearance rate of the pituitary glycoprotein hormone, LH, from the blood is under study. LH is the principal hormone regulating secretion of androgenic steroid by the testes. Previous work in our laboratory has demonstrated some diminution in the magnitude and a delay in the timing of evoked serum LH peaks when aged men were given LHRH (luliberin), the pituitary releasing factor for LH. In the present investigation we hope to clarify whether the observed alterations in LH secretory dynamics represent changes in the secretory response of pituitary gonadotrophs, in the rate of disposal of serum LH, or a combination of both these factors. This investigation is being done in Baltimore Longitudinal Study subjects as was the original work on LH secretory response.

Thyroid hormone secretory dynamics and the thyroid status of BLS men in the basal state has been the focus of another investigation in which subjects of various ages have been given constant infusion of TRH, (the hypothalamic releasing factor for pituitary TSH, which in turn controls thyroid function). Numerous previous papers have suggested that diminished thyroid function recurs in aging men, but other investigators have suggested that thyroid impairment is limited to aging subjects with either intercurrent illness or diagnosable thyroid disease. Preliminary analysis of our baseline data, obtained in screened, healthy BLS men, using a highly sensitive immunoassay, capable of detecting alterations of TSH within the normal range, suggests that serum TSH shows an upward trend with age concurrent with a small but statistically significant decrease in 3 independent indices of bioavailable thyroid hormone. These changes are what would be expected if there were a modest decrease in the secretory capacity of the thyroid gland in a significant number of aging men. It is important to note that none of the aging men studied was clinically or chemically hypothyroid. TSH responses to TRH infusion await analysis.

Samples are being obtained, but have not yet been analyzed, for a 5-6 year longitudinal follow-up of our previous study on aging effects on sex steroids and gonadotropins in BLS men. In that study, which received national attention from both professionals and laiety, we demonstrated that no "male menopause" occurred in healthy, active, middle class men from age 25-89. To confirm and extend this conclusion, which was obtained from a cross-sectional analysis of 76 men, we are collecting repeat serum samples on most of the same individuals in order to do longitudinal analysis. The major sex steroids and gonadotropins will be analyzed in these samples, and compared with the previous values.

The effects of illness on sex hormones are being studied as a compliment to the aging studies referred to above. It is hypothesized that some previous work showing sex steroid and gonadotropin alterations in aging men done by other investigators may have been influenced by the inclusion of subjects with significant chronic illness. Therefore, we have collected serum samples on men with a variety of malignant and non-malignant illnesses and are in the process of measuring testosterone, dihydrotestosterone, estrogene, gonadotropins, and indices of sex steroid protein binding in order to compare them with age-matched controls from our healthy BLS population.

Alterations in the hypothalamic-pituitary-gonadal axis in aging male rats in vivo are being investigated by measuring the turnover rates of norepinephrine and dopamine in hypothalamic nuclei controlling LHRH release. The concentration of LRH in the median hypothalamic area, and the affinity and capacity of pituitary cell membranes for LHRH in rats of various ages. Preliminary results show a small but significant decrease with age in stored LHRH in the hypothalamus, diminished synthesis (i.e., reduced turnover) of norepinephrine in the paraventricular and arcuate nuclei of the hypothalamus, and no age change in the affinity or binding capacity of pituitary cells for LHRH. Castration of the rats results in depletion of hypothalamic LHRH to similar levels in old and young rats and similar increases in pituitary binding capacity for LHRH, which, however, appear to occur later in the older rats. Thus, data indicate subtle age-associated alterations in both the hypothalamus and pituitary

Studies of the hypothalamic-pituitary-gonadal axis in aging female rats have been initiated using a complex in vivo model, in which phase of the estrous cycle (estrus, metestrus, or diestrus) according to vaginal cytology pattern. Blood levels of estrogen, progesterone, androgens, gonadotropins and prolaction, LHRH and catecholamine content of various hypothalamic nuclei, and binding affinity and capacity of LHRH receptors will be measured at each phase of the estrous cycle.

We have also initiated investigations of the affects of aging on the synthesis of the glycoprotein hormones LH and FSH by isolated pituitary cells in vitro. This work follows on our demonstration that isolated pituitary cells from old rats secrete less LH and FSH in response to LHRH and show unbalanced secretion of pituitary hormone subunits. These new investigations will use pulse chase techniques and a family of antibodies directed at various moieties of the glycoprotein subunit molecules to determine whether aging defects occur at the translational, post-translational processing (i.e., glycosylation) or secretory phases of gonadotropin production. No results have been obtained to date.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF** **INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 AG 00011-10 CPB

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)
Hormones, hormone receptors, and aging I. Aging and hormone-sensitive adenylate cyclase.

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	E. M. Dax	Visiting Associate	CPB	NIA
	C. R. Schneyer	Clinical Associate (Resigned 6/30/82)	CPB	NIA
	R. I. Gregerman	Chief, Endocrinology Section	CPB	NIA

COOPERATING UNITS (if any)

Department of Surgery, Baltimore City Hospitals

LAB/BRANCH
Gerontology Research Center, Clinical Physiology Branch

SECTION
Endocrinology Section

INSTITUTE AND LOCATION
NIA, NIH, Baltimore, Maryland 21224

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☒ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

These studies deal primarily with influences of age on the biochemistry of hormone-sensitive adenylate cyclase in a variety of tissues. The purpose of these studies is to explore the mechanisms of age-related alterations of hormone responsiveness and biological membranes, with special emphasis on the relationship between adenylate cyclase and hormone receptors. Other aspects include ongoing literature review of the field of aging and hormones in general and of certain aspects of clinical medicine as they relate to aging and endocrinology.

PHS-6040
(Rev. 2-81)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF** **INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 AG 00012-10 CPB

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Hormones, hormone receptors and aging. II. Aging and hormone responsiveness.

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	G. S. Roth	Research Chemist	CPB	NIA
Other:	M. Haji	Visiting Fellow (EOD 7/82)	CPB	NIA
	B. Baum	Dental Officer	PCB	NIDR
	J. Rifkind	Research Chemist	LBS	NIA
	M. Blackman	Guest Scientist	CPB	NIA
	S. M. Harman	Senior Investigator	CPB	NIA

COOPERATING UNITS (if any)

LAB/BRANCH
Gerontology Research Center, Clinical Physiology Branch

SECTION
Endocrinology Section

INSTITUTE AND LOCATION
NIA, NIH, Baltimore, Maryland 21224

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☒ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project is mainly involved in relating age, the various components mediating hormone actions (including receptors) and the biological responsiveness of hormone sensitive tissues.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 AG 00013-08 CPB

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)
Hormones, hormone receptors, and aging. III. Aging and human endocrine regulation.

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	S. M. Harman	Senior Investigator	CPB	NIA
OTHER:	R. A. Cropper	Clinical Staff Fellow (EOD 6/29/82)	CPB	NIA
	R. E. Wehmann	Staff Fellow (Resigned 7/1/82)	CPB	NIA
	M. R. Blackman	Guest Scientist	CPB	NIA
	P. T. Costa	Senior Investigator	LBS	NIA

COOPERATING UNITS (if any)

Dept. of Medicine, Baltimore City Hospitals

LAB/BRANCH
Gerontology Research Center, Clinical Physiology Branch

SECTION
Endocrinology Section and Human Performance Section

INSTITUTE AND LOCATION
NIA, NIH, Baltimore, Maryland 21224

TOTAL MANYEARS: 2.5	PROFESSIONAL: 2.3	OTHER: 0.2

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

These studies gather data on function of pituitary gonadal and pituitary thyroid endocrine systems in normal aging men in the Baltimore Longitudinal Study on Aging (BLSA). Measurements of pituitary response to hypothalamic releasing factors and of metabolic processing of glycoprotein hormones as well as circulating levels of sex steroid hormones and their relationship to sexual behavior in aging men are being undertaken.

PHS-6040
(Rev. 2-81)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 AG 00023-07 CPB

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)
Hormones, hormone receptors, and aging. Testis, pituitary, and hypothalamic function in aging and uremia.

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	S. M. Harman	Senior Investigator	CPB	NIA
OTHER:	R. A. Cropper	Clinical Staff Fellow (EOD 6/29/81)	CPB	NIA
	M. R. Blackman	Guest Scientist	CPB	NIA

COOPERATING UNITS (if any)
G. Briefel, Dept. of Medicine, Nephrology Section, Baltimore City Hospitals
P. Wise, Dept. of Physiology, University of Maryland School of Medicine

LAB/BRANCH
Gerontology Research Center, Clinical Physiology Branch

SECTION
Endocrinology Section

INSTITUTE AND LOCATION
NIA, NIH, Baltimore, Maryland 21224

TOTAL MANYEARS: 2.0	PROFESSIONAL: 1.2	OTHER: 0.8

CHECK APPROPRIATE BOX(ES)
☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Secretory cells from rat gonads and pituitaries are studied in vitro to compare their physiology in old and young rats and in normal vs. uremic rats. Testosterone production, in response to gonadotropin and to dibutyryl cAMP and cell number of gonadotrophin receptors, are measured in order to investigate alterations of Leydig cell function. Production of TSH in response to TRH, production of LH and FSH and their subunits in response to LRH and receptors for LRH have been measured in order to investigate altered function of pituitary secretory cells. Hypothalamic content of LRH, and turnover rates of dopamine and catecholamines in hypothalamic nuclei are being determined. Deficient function of aged pituitary cells in vitro has been found as has a reduction in LRH receptor affinity. Castration increases LRH responsiveness of gonadotrophs of aged and young rats to the same extent.

PHS-6040
(Rev. 2-81)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01-AG-00093-10-CPB

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)
Cellular Basis of Regulation of the Humoral Immune Response

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	A. A. Nordin	Research Chemist	CPB NIA
	J. Curtis	Medical Staff Fellow	CPB NIA EOD 7/81

COOPERATING UNITS (if any)
None

LAB/BRANCH
Gerontology Research Center, Clinical Physiology Branch

SECTION
Clinical Immunology Section

INSTITUTE AND LOCATION
NIA, NIH, Baltimore, Maryland 21224

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
3.4	1.6	1.8

CHECK APPROPRIATE BOX(ES)
☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The regulatory mechanisms of lymphoid cells are being investigated in vitro using a T-cell dependent as well as a T-cell independent antigen. The cellular requirements and functions involved in the in vitro immune response are being established for normal adult mice. These are then being compared to those in aged mice of the same strains. The possibility that regulatory mechanisms observed in young adult mice are amplified in old mice resulting in immunosenescence is being investigated.

PHS-6040
(Rev. 10-76)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01-AG-00095-09-CPB

PERIOD COVERED
October 1, 1981 - September 30, 1982

TITLE OF PROJECT (80 characters or less)

The Role of Cell Membrane Structures on Cellular Recognition

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	W. H. Adler	Medical Officer, PHS	CPB NIA
Other:	J. E. Nagel	Medical Officer, PHS	CPB NIA
	R. K. Saxena	Visiting Associate	CPB NIA
	Q. B. Saxena	Visiting Associate	CPB NIA
	R. Yanagihara	Clinical Associate, PHS	CPB NIA-left 6/11/82
	J. Curtis	Medical Staff Fellow	CPB NIA EOD 7/81
	M. A. Brock	Biologist	CPB NIA

COOPERATING UNITS (if any)

None

LAB/BRANCH
Gerontology Research Center, Clinical Physiology Branch

SECTION
Clinical Immunology Section

INSTITUTE AND LOCATION
NIA, NIH, Baltimore, Maryland 21224

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
4.7	3.4	1.3

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The project will define the functional capability of lymphocyte subpopulations in young and aging mice. Assays for functional ability and techniques for cellular manipulation allow for correlation of type of cell with particular function. The use of cell sorting apparatus will facilitate separation of subpopulations of cells in lymphoid tissue. The analysis of cellular function in aging animals will delineate the basis of the age associated decline in immune function.

PHS-6040
(Rev. 10-76)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01-AG-00096-09-CPB

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)
Low Temperature Effects on Cells of Aging Individuals

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I:	M. A. Brock	Research Biologist	CPB NIA
Other:	W. H. Adler	Medical Officer, PHS	CPB NIA

COOPERATING UNITS (if any)
None

LAB/BRANCH
Gerontology Research Center, Clinical Physiology Branch

SECTION
Clinical Immunology Section

INSTITUTE AND LOCATION
NIA, NIH, Baltimore, Maryland 21224

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.1	1	.1

CHECK APPROPRIATE BOX(ES)
☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The objectives of this project are to characterize age-related differences in the in vitro responses of murine lymphohemopoietic cells to mitogens and their differential susceptibility to freezing damage. Because there are optimal cooling velocities for the cryopreservation of each cell type, T- and B-lymphocytes from young animals can be recovered with slight impairment of function using an optimal cooling rate. Changes in cellular structure and/or function with age then may be distinguishable with selective freezing injury to one or both subpopulations. Structures considered the probable sites of freezing damage are the plasma membrane and cellular membrane systems.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01-AG-00104-06-CPB

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Clinical Immune Survey of the Longitudinal Project Participants

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	W. H. Adler	Medical Officer, PHS	CPB NIA
Other:	A. A. Nordin	Research Chemist	CPB NIA
	J. E. Nagel	Medical Officer, PHS	CPB NIA
	Q. B. Saxena	Visiting Associate	CPB NIA
	J. L. Curtis	Medical Staff Fellow	CPB NIA EOD 7/81

COOPERATING UNITS (if any)

None

LAB/BRANCH
Gerontology Research Center, Clinical Physiology Branch

SECTION
Clinical Immunology Section

INSTITUTE AND LOCATION
NIA, NIH, Baltimore, Maryland 21224

TOTAL MANYEARS: 3.55	PROFESSIONAL: 1.75	OTHER: 1.8

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☒ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The immune function of participants in the Baltimore Longitudinal Study of Aging is evaluated to determine age-associated changes and the possible effects of these changes on the incidence and type of disease. Another major goal is to evaluate the ability of existing assays of immune function to provide an accurate assessment of the level of immune competence of aging individuals and to refine and develop new methods and assays to evaluate any elderly individuals host defense mechanism.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)

U.S. DEPARTMENT OF
HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NOTICE OF
INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00015-24 CPB

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

The Baltimore Longitudinal Study of Human Aging

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	R. Andres	Chief, Clinical Physiology Branch	CPB NIA
	J. D. Tobin	Chief, Human Performance Section	CPB NIA
	N. W. Shock	Scientist Emeritus	NIA
	S. K. Sharma	Sociologist	CPB NIA
OTHER:	L. Brant	Mathematical Statistician	CPB NIA

Other workers who are associated with the Longitudinal Study describe their involvement in their individual reports.

COOPERATING UNITS (if any)

Baltimore City Hospitals

LAB/BRANCH
Gerontology Research Center, Clinical Physiology Branch

SECTION
Human Performance Section

INSTITUTE AND LOCATION
NIA, NIH, Baltimore, Maryland 21224

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The Baltimore Longitudinal Study of Human Aging (BLSA) serves as a resource for scientists working in the field of Gerontology. It provides a well-described group of men and women between 20 and 96 years of age for studies of the mechanisms of human aging. Projects in physiology, biochemistry, psychology, nutrition, pharmacology, endocrinology, sociology, and genetics, have been carried out or are in progress.

Objectives: The BLSA provides a well described group of subjects as a resource in support of a wide variety of scientific investigations in gerontology and other disciplines. While long-term planning is encouraged, important studies of shorter duration have also been undertaken. The long-term general goals of the project are to: (1) secure replicate measures of physiological, pathological, biochemical and psychological variables on longitudinal study participants at specified intervals; (2) summarize and compare the results of testing in relation to age according to cross-sectional and longitudinal formats; (3) identify characteristics of individual participants which may be related to changes of function over time and to age at death; and, (4) determine whether the data obtained support one or another theory of the mechanisms responsible for age-related functional decrements.

Methods Employed: The Sample: Study participants are male and female volunteers recruited by other participants in the program. Recruits agree to return to GRC in Baltimore for 2-1/2 days of testing every two years for an indeterminate period. Our sample continued to be highly educated, mostly married, describing themselves as financially comfortable or better, and of the group who returned for the fifth visit, 90% rated their health as good or excellent on both first and fifth visits. The age distribution of the active subjects is shown in Table 1.

Table 1: Distribution of the Active Subjects by Age and Sex (in percent).

Age Group	Sex	
	Men	Women
> 20	0.2	0.3
20-29	3.4	7.1
30-39	15.1	15.9
40-49	14.7	16.2
50-59	18.8	18.1
60-69	21.2	21.4
70-79	15.7	17.5
80-89	9.5	3.2
90+	1.3	0.3

Data Management: Medical records and test results are maintained in written form in the laboratory and transferred to a data retrieval and analysis system by keypunching on tabulation cards or by recording the test results directly on punched paper tape or magnetic tape. Data are maintained and used in ways which protect the privacy of participants. Sensitive material is specially encoded. Individual scientists review, evaluate and summarize the data for scientific reporting.

Major Findings: By August 5, 1982 a total of 1159 men and 342 women have participated in the testing program on one or more visits to the GRC. Since the inception of the study 259 men have died. As of August 5, 1982, 900 men have completed three or more visits for testing, 684 visited five times or more, 330 ten times or more, 188 twelve times or more, and

55 fifteen times or more. In all, these subjects account for a grand total of 7678 participant visits.

During the year, 42 women were newly admitted to the program as compared to 17 men. Of the 342 women who have joined the BLSA since January 1978, four have died and 29 withdrew or failed to return, leaving an active sample of 309. One hundred ninety-one (191) women have been tested two times; 97 have been tested three times or more.

The Illness and Disability Study (I&D) continues to be an integral part of the BLSA.

The objectives of the "Illness & Disability Study" are: 1) to determine the alive/dead status of those subjects who dropped out from the BLSA between 1958 and June 30, 1977 (N=280); 2) to locate and contact these subjects and gather information pertaining to their health and illness experience subsequent to their dropping out from the BLSA; 3) to ascertain the risk factors for dropping out from the BLSA and to recommend control measures directed toward attaining maximum participation; 4) to determine whether subjects who dropped out differed significantly from those subjects who remained active in the study with regard to health.

As of July 1, 1977, there were 1088 subject who had made one or more visits to the BLSA since the inception of the study in February 1958. Of those 1088, six hundred and fifty-nine (60.5%) were still active in the study. One hundred and fifty-seven (14.4%) failed to return to the BLSA. One hundred twenty-three (11.3%) formally withdrew from the BLSA. The remaining one hundred and fifty (16.3%) were known to be dead as of July 1, 1977. (Table 2)

Table 2: Frequency Distribution of BLSA Subjects by Status
N = 1088 (July 1, 1977)

Status	No.	Percent
Active	659	60.48
Failure	157	14.43
Withdrawn	123	11.30
Deceased	150	13.70
	1088	100.00
Total attrition in 20 years by reason other than death		25.73%
Annual attrition rate		1.29%

Methods: First, an attempt is made to locate all the drop-outs (those who have failed to return for tests and those who have formally withdrawn). After the subjects are located, a letter is mailed to the subjects explaining this study and requesting their cooperation. This letter is followed by a telephone call approximately 10 days after the letter is mailed. Subjects are encouraged to return to the BLSA, for one or more visits. If the subject can not come to the BLSA for any reason, an attempt is made to get their consent for a home visit by the investigator. If a home visit is not possible (due to distance), an attempt is made to get consent for an Interval Medical History by mailed questionnaire. In addition, these subjects are asked to provide consent for the investigator to obtain information from any physician/s and hospitals that they may have visited during this interval period. If the subject refuses the questionnaire, an attempt is made to get consent for a telephone interview.

The results with regard to the first two objectives are summarized first. All but three (1.1%) subjects have been located. Fifty-eight (20.7%) had died subsequent to their dropping out from the BLSA. Of the remainder two hundred seventeen (77.5%) subjects who were found to be alive, seventy-eight (35.9%) returned for another visit to the BLSA, thirty-nine (17.8%) were visited in their own home by this investigator, seventy-one (32.7%) responded to a mailed questionnaire, sixteen (7.4%) responded to a telephone conversation, two (.9%) have agreed to cooperate and will make a decision in the near future about manner of cooperation. Only two (0.7%) subjects refused to cooperate while one subject was dropped from the study for administrative reasons at the beginning of the study.

To ascertain the risk factors for dropping out from the BLSA, the influence of age, marital status, education, occupation, distance between a subject's residence and study center, self-health and financial assessment (all measured at first visit) and method of recruitment on attrition was examined. the 1088 subjects who joined the BLSA during the first twenty years (1958-1977) were studied using a multiple logistic regression model. To control for death, two separate analysis were performed. Both analysis produced similar results with the exception of age not being significant when accounting for death. The analysis shows that subjects 70 years and older with less than Bachelors degree, living 500 miles or more from study center, perceiving their health as average or below and recruited by another subject who in turn has dropped out has the greatest risk of dropping out (3.5 fold). Recruiter's status shows the strongest association with the standardized risk ratio indicating a reduction in the average risk of 20% among subjects recruited by a fellow subject who remains active, while there is a two fold increase in the average risk among those whose recruiter drops out. These findings have important implications with regard to minimizing future attrition in the following ways: Identification of recruiter's status as the most important risk factor enables us to identify "population at risk" for dropping out. This can be used to suggest a number of stategies aimed at minimizing subsequent attrition.

Future plans include: 1) similar analysis using psychological and physical health data; 2) using Cox's Hazard Function, a survivorship analysis will be performed; 3) operationally, mechanisms for future contact with drop-out has been established as a result of this study. Drop-out occuring since June 30, 1977 will be contacted in a similar manner. 4) Data on subsequent health and illness experiences of dropouts will be analyzed. 5) Using the experience of male drop-out study, a method is established both operationally and conceptually for locating and contacting women drop-outs.

Statistical Consultation: The statistical activity of the Human Performance Section (HPS) provides statistical consultation to other sections involved in the BLSA as well as many other GRC investigators. One important effort was collaboration on a study of attrition among BLSA participants. Other routine consultations have been associated with research on bone and hand data, cardiovascular, body composition, and sex data pertaining to BLSA as well as other longitudinal animal data and human behavioral data of other GRC studies. Also computer algorithms and programs have been written to do specially formulated statistical analyses needed by many scientific investigators. These programs fill needs not presently available via packaged statistical programs and increase the effectiveness of the research effort.

Significance to Bio-Medical Research and the Program of the Institute: A major goal of the longitudinal program is a deeper understanding of age-related changes in the different organ systems, and their interrelationships. The relation of functional changes in an individual to age at death, age at onset of a disease, and other end points is important for understanding aging in humans and the impact of aging on society. The intensive study of multiple variables will also provide tests of risk-factor theories for specific age-related diseases.

Proposed Course: Data collection and analyses will be continued. Continued emphasis on automation of tests, data entry, and analyses should provide improved accuracy and efficiency. A major summary of all aspects of this program is in progress.

Publications:

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 AG 00018-16 CPB

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Marital, Sexual and Social Factors in Aging

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	C. Martin	Sociologist	CPB NIA
OTHER:	Paul Ephross	School of Social Work and Community Planning, University of Maryland at Baltimore	
	Jan D. Sinnott	Department of Psychology, Towson State University	

COOPERATING UNITS (if any)

Baltimore City Hospitals

LAB/BRANCH
Gerontology Research Center, Clinical Physiology Branch

SECTION
Human Performance Section

INSTITUTE AND LOCATION
NIA, NIH, Baltimore, Maryland 21224

TOTAL MANYEARS: 0.80	PROFESSIONAL: 0.70	OTHER: 0.10

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☒ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The investigator has now interviewed nearly 800 BLSA males with regard to their history of marriage and sexual activity. Two types of data analysis were undertaken during the year. First, subjects with a history of prostatectomy and their controls were compared on some 114 attributes relating to medical status, many aspects of marital and sexual experience, and numerous measures of cognitive and physiologic function. Findings indicated that unstable coital and marital relationships, differing rates of sexual activity, and sexual attitudes and reactions are apparently unrelated to the genesis of benign prostatic hypertrophy. The second analysis concerned the question as to why males vary widely in frequency of sexual expression. An examination of numerous individual attributes by means of an analysis of variance model revealed that 4 variables could explain 48% of variance in current rates of activity. The predictive value of each variable varied widely, however, when the model was applied to relatively young, middle-aged, or old subjects.

Objectives: Present objectives are to: 1) determine whether BLSA males who acquire certain diseases or conditions of unknown etiology may differ from age-matched controls with respect to various characteristics of marital, sexual or social experience, 2) identify those factors which best predict the variation observed in current frequencies of sexual activity, and if possible, determine which physiologic and cognitive factors are responsible for that variation, and 3) interview the few men remaining in the program who have not been interviewed.

Methods Employed: In requesting interviews, the investigator describes study objectives in considerable detail, provides assurance concerning confidence, and emphasizes the voluntary nature of such a contribution. Over the years the refuse rate has remained at 2 to 3 percent.

To aid communication and to insure systematic data collection, the questions asked were all memorized by the investigator along with appropriate categories for the recording of responses. In establishing rapport and generating data not otherwise obtained, various aspects of residential, occupational, religious, military, and parental-home experience are reviewed before introducing questions relating to marital adjustment and sexual conduct. The information secured is in many ways unique and is believed to be of unusual quality because of the excellent mental status of respondents and their evident interest in this part of the BLSA program.

Major Findings: During the year, two kinds of data analysis were undertaken. First, in a search for risk factors in benign prostatic hypertrophy (BPH), in collaboration with Dr. Paul Ephross, 68 BLSA men with a history of prostatectomy were compared with 136 age-matched controls with respect to more than one hundred attributes, including various aspects of marital and sexual experience, diagnostic status in regard to coronary disease, and a wide array of measures of cognitive and physiologic function. From these comparisons, 5 factors emerged as significant correlates of BPH; namely, lower body weight, smaller chest circumference, cessation of coitus at an older age, more frequent intoxication, and a lesser inclination to view regular sexual activity as important for good health. It is possible, of course,, that BPH or its treatment by surgery may have reduced body weight and that alcohol is a risk factor for this condition. However, given the number of variables examined, this number of significant findings could be expected purely by chance. In a more positive vein, present findings are of interest in that they fail to support the assumption that unstable marital or coital relationships, or that individual differences in regard to quantity of sexual activity, erotic responsiveness and motivation are involved in the etiology of BPH.

The second analytic problem, undertaken with the help of Dr. Jan D. Sinnott, dealt with the issue of identifying factors which will predict, or perhaps explain, why males differ in frequency of sexual expression. Stable values of measures of body composition, and of physiologic and cognitive function were based on tests administered to respondents on three separate visits surrounding the time of interview. The dependent variable used was "the number of sexual events reported for the year prior to interview" (FREQSX).

Since subjects varied from 23 to 79 years of age and many of the independent variables of interest are closely related to age, a "packaged" computer program (SAS-General Linear Model) was selected--a multiple regression program that generates SUMS of squares which reflect the relative contributio of each variable to total variance when the effect of all other variables in the model are partialled out. As a result of relating each independent variable to FREQSX in combination with age, by means of the model, the number of significant predictors of FREQSX was reduced to 20 after the effect of age was removed. These factors, again related to FREQSX in various combinations, generated a 4-variable model which accounted for 48 percent of total variance. In decreasing order of importance, the four variables were "time comfortable without sex" (INTERVAL), age (AGE), "customary frequency of coitus in early marriage" (EARLY C), and potency status (POTENCY).

The four variables selected by this procedure are familiar and comprehensible elements of male sexual functioning and readily fall into a general explanatory model. However, the model proved disappointing in that none of the many physiologic and cognitive variables examined were among the major predictors of sexual frequency. When the variables of INTERVAL and EARLY C were excluded from the analytic model, the following variables emerged as significant factors in explaining variance: higher basal metabolic rate, fewer errors on the Benton Visual Retention Index, and greater grip strength, right hand. On the other hand, the increase in variance explained by these three factors was only 5 percent or less, in addition to age alone.

Significance to Bio-Medical Research and the Program of the Institute: One assumption behind the above cited analysis is that if factors responsible for individual differences in sexual functioning can be identified, they may prove useful in explaining why male sexual vigor declines with age. In general, the factors appearing in the predictive model contribute to our understanding of the importance of and interactions between certain subjective and functional aspects of sexual behavior.

Proposed Course: In further pursuit of the questions noted, a next step is to consider, in turn, factors other than sexual frequency as dependent variables in anticipation of implicating still other predictive and explanatory models.

Publications: Martin, C.E.: Factors affecting sexual functioning in 60-79 year old married males. Archives of Sexual Behavior 10:399-420, 1981.

Tsitouras, P.D., Martin, C.E., and Harman, S.M.: Relationship of serum testosterone to sexual activity in healthy elderly men. Journal of Gerontology. 37:288-293, 1982.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 AG 00021-19 CPB

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)
Study of Normal Human Variance: 1. Dermatoglyphics 2. Lateral Dominance 3. Visual Function 4. Color Vision

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	C.C. Plato	Geneticist	CPB NIA
OTHER:	D.C. Gajdusek	Chief, Lab. of Central Nervous System Studies	CNS NINCDS
	R. Garruto	Sr. Staff Associate	CNS NINCDS
	K.M. Fox	Biologist	CPB NIA
	K. Kimura	Guest Scientist	CPB NIA
	N. Gittings	Psychologist	CPB NIA

COOPERATING UNITS (if any)
See attached page.

LAB/BRANCH
Gerontology Research Center, Clinical Physiology Branch

SECTION
Human Performance Section

INSTITUTE AND LOCATION
NIA, NIH, Baltimore, Maryland 21224

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.75	0.50	0.25

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project represents A) an ongoing joint collaborative effort, involving the WHO and other national and international biological laboratories to coordinate the collection, evaluation and interpretation of dermatoglyphic data. Specifically the objectives of this project are: 1) to establish dermatoglyphic markers in various diseases (clinical dermatoglyphics); 2) to establish the dermatoglyphic frequencies in normal control samples (control dermatoglyphics); 3) to study the distribution of dermatoglyphics among the various human populations (population dermatoglyphics); 4) to study the dermatoglyphics of the aged: 5) to study the genetics of dermatoglyphics; and, 6) to utilize dermatoglyphics as an added tool in twin diagnoses (twin dermatoglyphics). B) Evaluation of lateral functional dominance among BLSA participants. C) Cross sectional and longitudinal study of visual function in BLSA participants.

Cooperating Units:

1. W. Wertelecki
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University of South Alabama
Mobile, Alabama

2. J. T. Schwartz
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Bureau of Medical Services
Health Service Administration
USPHS, West Hyattsville, Maryland

3. R. MacLennan
International Agency for Research on Cancer
WHO, Lyon, France

4. M. Alpers
Institute of Medical Research
Goroka, New Guinea

5. C. Bartsocas
Department of Pediatrics
University of Athens
Athens, Greece

6. T. Kuberski, Epidemiologist
NIMDD, Epidemiology and Field
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7. M. T. Newman
Department of Anthropology
University of Washington
Seattle, Washington

8. R. W. Hornabrook
New Guinea Institute of Medical Research
Wadestown, Wellington, New Zealand

9. Y. Ahuja
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16. Paul Tchen
Groupe De Recherches De Genetique Epidemiologique
Paris, France

Project Description:

Objectives: A) the ongoing dermatoglyphics project represents an extensive collaborative effort in conjunction with WHO and other national and international institutions, to study all aspects of dermatoglyphics. The specific objectives of this study are: 1) To utilize dermatoglyphic markers in clinical investi-gations, 2) To establish dermatoglyphic frequencies in non-affected, control samples from different human populations, 3) To utilize dermatoglphic markers in studies of population genetics, twin diagnosis and other genetic investigations. 4) To determine possible effects of chemical pollutants,on embryonic development through dermatoglyphic anomalies. B) To establish the hand, foot and visual lateral dominance in BLSA participants in an effort to understand the normal physiological and anatomical bilateral asymmetry. C) to establish cross sectional age specific visual function levels in BLSA participants and investigate through longitudinal studies the changes in visual function.

Methods Employed: Digital and palmar prints collected by different groups through various methods are sent to our laboratory for evaluation and interpretation of the results. We developed new methods and computer programs for studying and analyzing the dermatoglyphic data. These methods have been accepted and are utilized by other laboratories here and abroad.

In order to determine lateral functional dominance the participants were requested to perform seventeen tasks. Two of these relate to single hand involvement; two tests related to single hand fine manipulation; three tasks involve fine function of one hand with significant assistance from the subordinate hand; three tasks are single handed activities which involve whole body movement. In addition to these handedness tests, the participants were tested for foot dominance, eye dominance (Dolman test), digital interlocking, arm folding and foot overlapping. At the completion of these tests the participant is asked whether he considers himself/herself as left handed, right handed or ambidextrous. Many participants were tested in more than one visit to determine repeatability of the tests.

Vision tests are administered with a Titmus optical vision tester which simulates vision at both 20 feet and 14 inches. Acuity is measured with both Sloan letters and Landolt Rings. Depth perception and vertical and lateral phorias are assessed. The subject is tested with glasses, if he or she wears them as well as without glasses. Color discrimination is tested with the American Optical Pseudo Isochromatic Plates.

Major Findings: 1) Significant differences were found in the digital pattern frequencies of patients with breast cancer, individuals with high risk for developing breast cancer and non-affected controls. Patients have the highest frequency of whorls and controls the lowest. The frequency of whorls in the high risk category, which is defined as having positive family history, nulliparity or severe fibrocystic mastopathy, falls between those of the patients and controls. Furthermore, 95% of all subjects with six or more whorls were either cancer patients or high risk individuals. An expanded investigation is now underway, which includes palmar dermatoglyphic evaluations and ridge counts, in an effort to confirm the findings of the present pilot study. 2) It is usually assumed that the more variables investigated, the higher will be the accuracy of handedness determination. The results of our study, which utilized ten different tests for hand dominance determination suggested that, unless one is interested in a specific type of hand dominance, an accurate determination of handedness may be made by simply testing for hand writing or by asking the participants if they are left or right handed. Utilizing a battery of lateral dominance tests may add very little information to the overall determination of handedness and, in the case of the two-handed functions with whole body movement, batting (baseball) and putting (golf), may contribute misleading information.

Significance to Biomedical Research and the Program of the Institute: Dermatoglyphics are valuable genetic markers utilized in investigating the etiology of clinical entities. Dermatoglyphics are genetically determined, mostly through multiple genes. They are nevertheless vulnerable to intrauterine disturbances up to the time of their final development. Once development is completed between the 3rd and 4th month of pregnancy, dermatoglyphics remained unchanged (except for size) throughout the individual's life time. Dermatoglyphics, therefore, reflect effects of genetic anomalies, diseases or intrauterine disturbances, affecting the embryo during the first trimester of pregnancy. A final advantage in using dermatoglyphics in research is their uniqueness. That is, no two individuals (including identical twins) have identical dermatoglyphics.

Handedness and lateral dominance in general are easily identifiable manifestations of cerebral dominance. The results of the lateral dominance tests provide additional genetic polymorphic data, contribute to our efforts to understand normal anatomical asymmetry and may offer clues into the etiology of anomalies demonstrating bilateral asymmetry or unilateral occurrence.

Proposed Course: To continue the analysis of the collected data and publish the results. To expand the study of possible associations between dermatoglyphics and breast cancer and diabetes in order to confirm the preliminary findings. To ascertain the dermatoglyphic frequencies of coronary heart disease and cancer of all types among BLSA participants as well as among participants of collaborative units. To continue the population and genetic dermatoglyphic analysis for characterization of appropriate control samples. To finish the analysis of the lateral dominance and visual function data of the BLSA participants and prepare reports for publication.

Publications:

Hoff, C., Plato, C.C., Garruto, R.M. and Dutt, J.: Dermatoglyphic assessment of the genetic relationships of negative American populations. Am. J. Phys. Anthrop. 55:455-461, 1981.

Plato, C.C. and Wertelecki, W.: Changing Trends in Dermatoglyphic Research. In Partsocas, C.S. (Ed.): Progress in Dermatoglyphic Research. New York, Alan R. Liss, Inc., 1982, pp. 1-12.

Wertelecki, W. and Plato, C.: Dermatoglyphic Research and the Clinician. In Bartsocas, C.S. (Ed.): Progress in Dermatoglyphic Research. New York, Alan R. Liss, Inc., 1982, pp. 25-32.

Bartsocas, C.S., Panayotou, T., Voronas, S., Kritsikis, S., Plato, C.C. and Papadatos, C.J.: Digital and Palmar Dermatoglyphics in Greeks. In Bartsocas, C.S. (Ed.): Progress in Dermatoglyphic Research. New York, Alan R. Liss, Inc. 1982, pp. 247-268.

Plato, C.C. and Fox, K.M.: Measures of lateral functional dominance. I. Hand dominance. Neuropsychologia. In Press.

Plato, C.C., Garruto, R.M. and Gajdusek, D.C.: Further studies on the genetics of the Chamorros of Guam. Human Heredity. In Press.

Seltzer, M.H., Plato, C.C., Engler, P.E., and Fletcher, H.S.: Digital and palmar dermatoglyphics and breast cancer. Breast Cancer Research and Treatment. In Press.

Larrick, J.W. and Plato, C.C.: Digital and palmar dermatoglyphic patterns among natives of extreme horthwest Nepal. Human Heredity. In Press.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 AG 00022-06 CPB

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Investigations of Osteoarthritis and Bone Loss

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	C.C. Plato	Geneticist	CPB NIA
	J.D. Tobin	Chief, Human Performance Section	CPB NIA
OTHER:	D.C. Gajdusek	Chief, Lab. of Central Nervous Systems Studies	CNS NINCDS
	R.M. Garruto	Sr. Staff Associate	CNS NINCDS
	W.W. Greulich	Dept. of Anatomy, Stanford U.	
	R.T. Yanagihara	NINCDS Research Center, Guam	NINCDS
	F.E. Purifoy	Staff Fellow	CPB NIA
	K.M. Fox	Biologist	CPB NIA
	K.M. Chen	NINCDS Research Center, Guam	NINCDS

COOPERATING UNITS (if any)
Tecumseh Michigan Community Health Study
The University of Michigan, Ann Arbor, Michigan

LAB/BRANCH
Gerontology Research Center, Clinical Physiology Branch

SECTION
Human Performance Section

INSTITUTE AND LOCATION
NIA, NIH, Baltimore, Maryland 21224

TOTAL MANYEARS: 1.5	PROFESSIONAL: 0.70	OTHER: 0.85

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Osteoarthritis and bone loss are the two principal age related changes of the human skeleton. Even though these changes are considered inherent to aging, they may result in incapacitating ailments. The advanced cases of osteoarthritis (degenerative joint disease) produce severe restriction of movement associated with pain. Advanced bone loss may result in osteoporosis and frequent bone fractures. Most prominent are vertebral compression fractures and fractures of the femoral neck. The following skeletal sites are involved in the present study: hand-wrist, ulna and radius and vertebral column. This project deals with the epidemiological, genetic and longitudinal aspects of osteoarthritis and bone loss among (1) the participants of the Baltimore Longitudinal Study, (2) in a sample of normal Guamanians (Chamorros), (3) among patients afflicted with Amyotrophic Lateral Sclerosis/Parkinsonism Dementia Complex of Guam.

Project Description: Z01 AG 00022-06 CPB

Objectives: The objectives of this study are: 1) To study the cross-sectional and longitudinal changes in bone measurements, bone mineral content and bone loss at different parts of the skeletal system of male and female participants of the BLSA and to identify factors which may affect them. 2) To evaluate the cross-sectional longitudinal and bilateral aspects of osteoarthritis in the digits and the vertebral column. 3) To compare age of onset and rate of bone loss between BLSA male and female participants and other populations. 4) To investigate the longitudinal, familial and secular changes in bone measurements and bone density by examining Guamanian x-rays of the same individuals collected 33 years apart. 5) To study a) the possible differences in bone density between patients with Amyotrophic Lateral Sclerosis/Parkinsonism Dementia Complex (ALS/PD) of Guam and a non-affected Guamanian sample and b) the effect of long term immobilization, due to paralysis, on bone mineral content. and c) to study the relationship between radiographical evaluation of bone mineral content and calcium metabolism assays.

Methods Employed: Bilateral radiographs of the hand and wrist from BLSA participants, from Guamanian patients affected with Amyotrophic Lateral Sclerosis (ALS) or Parkinsonism Dementia (PD), and from non-affected adult Guamanians were evaluated for osteoarthritis and bone mineral content. All radiographs were obtained using similar film, at exposure of 1.0 second at 100 MA and 60 KVP without intensifying screens. Osteoarthritis grading of proximal, distal and metacarpophalangeal joints is carried out utilizing the internationally accepted grading system of Kellgren. Bone measurements, total width, medullary width and length, were done at the midshaft of the second metacarpal directly from the radiographs using vernier caliper. Cortical thickness was derived by subtracting medullary from the total width.

Major Findings: A) Evaluations of bone measurements of the second metacarpal, from hand-wrist x-rays of BLSA participants, showed that the total width and length of this bone do not change significantly with age once adulthood has been attained. What does change significantly with age, however, is the amount of bone mineral content (estimated through the combined cortical thickness), which is reduced due to bone resorption from the endosteal surface. The magnitude of the change is greater in females than in males, especially after the fifth decade of life, which suggests an interaction between female climacteric and those processes causing bone resorption. In general, the second metacarpal is larger and longer in males than females and the right hands than the left. Further analysis of the data, by hand dominance, suggested an inherent tendency for the right second metacarpal to have more bone than the left regardless of hand dominance. Differential stress, exerted on the bone by muscle, due to hand dominance will increase this bilateral difference among right handed and decrease it among left handed. B) Paired comparisons of bone measurements and bone demineralization between BLSA participants and individually matched Chamorros of Guam gave the following results: Chamorros of both sexes showed bilateral asymmetry in bone measurements and in the amount of cortical bone. Both Chamorro and Caucasian males

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had longer second metacarpals and more cortical bone than females. Caucasian males, however, had longer and larger second metacarpals than Chamorro males. Despite differences in the length and total width, Chamorro and Caucasian participants generally showed no significant differences in the amount of cortical bone or percent cortical area in the second metacarpal, suggesting that larger bones may not always indicate greater cortical mass. Although cross-sectional data suggested apparent age differences in the onset and rate of bone loss between Chamorros and Caucasians, the numbers of participants were too small to allow meaningful age by age statistical comparisons.

Significance to Bio-Medical Research and the Program of the Institute: Loss of bone tissue and deterioration of the joints are significant causes of disability and death in older people. Determination of the existence and degree of disease in relatively well ambulatory people provides a unique opportunity to compare bone loss and degeneration with other characterisitcs of these people. Nutrient intakes, activity levels and muscle strength among other things may be compared.

Proposed Course: We are presently continuing the studies of bone loss with age through 1) longitudinal analysis of BLSA data collected during the past twenty years, 2) determination of bone mineral content in the ulna and radius of BLSA participants, through photon absorptiometry, 3) further investigations in regards to the role of menopause and hormonal changes in the process of bone loss, 4) comparative studies of bone growth and loss in different human populations, 5) possible relationships with nutrient intakes, medications, socioeconomic stutus, physical activity, muscle strength and other physiological variables, 6) cross-sectional and longitudinal evaluation of bone loss in normal Guamanian Chamorros and patients suffering from Amyotrophic Lateral Sclerosis and/or Parkinsonism Dementia of Guam, and 7) analysis of family data especially sib pair and parent offspring correlations.

Publications:

Plato, C.C. and F.E. Purifoy: Age, sex and bilateral variability in bone loss and bone measurements of the second metacarpal. Growth. In Press.

Plato, C.C., R.M. Garruto, R.T. Yanagihara, K.M. Chen, J.L. Wood, D.C. Gajdusek and A.H. Norris: Cortical bone loss and measurements of the second metacarpal bone. I. Comparisons between adult Guamanian Chamorros and American Caucasians. Am. J. Phys. Anthrop.. In Press.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 AG 00028-06 CPB

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)
Epidemiological and Genetic Studies of Amyotrophic Lateral Sclerosis/Parkinsonism Dementia (ALS/PD) Complex of Guam

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	C.C. Plato	Sr. Research Geneticist	CPB NIA
OTHER:	D.C. Gajdusek	Chief, Lab. of Central Nervous Systems Studies	CNS NINCDS
	R.M. Garruto	Sr. Staff Associate	CNS NINCDS
	R.T. Yanagihara	Research Associate	CNS NINCDS

COOPERATING UNITS (if any)

C & F Research Center, NINCDS

LAB/BRANCH
Gerontology Research Center, Clinical Physiology Branch

SECTION
Human Performance Section

INSTITUTE AND LOCATION
NIA, NIH, Baltimore, Maryland 21224

TOTAL MANYEARS: .40	PROFESSIONAL: .20	OTHER: .20

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☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The purpose of this study is: 1) to investigate the genetic and epidemiological factors contributing to the very high incidence of Amyotrophic Lateral Sclerosis and Parkinsonism Dementia (ALS/PD) on Guam, 2) to evaluate the distribution of the various established genetic and anthropological markers among the normal Guamanian population and compare them with those of the ALS/PD patients, and 3) to ascertain the effects of immobilization due to paralysis on bone density.

Project Description: Z01 AG 00028-06 CPB

Objectives: Our involvement in this multidisciplinary project has the following objectives: 1) to determine the extent of genetic involvement in the etiology of amyotrophic lateral sclerosis and Parkinsonism Dementia (ALS/PD) complex of Guam. 2) to study the distribution of several established genetic markers such as blood groups, serum proteins, red cell enzymes and dermatoglyphics in the normal Guamanian (Chamorro) population to be used as controls in comparisons with patients, 3) to determine the prevalence of osteoarthritis, osteoporosis and other bone diseases in Chamorro ALS/PD patients and non-affected controls, and 4) to study bone growth and development of normal Guamanian children and adolescents in a 33 year follow-up study (See project #Z01 00022-06 CPB).

Methods Employed: Two separate approaches were followed in our efforts to ascertain the familial and genetic aspects of ALS/PD. First, the patient control registry panels (registries). The registries were initiated in 1958 and closed in 1963. At the time of their closing they consisted of 136 patients, 136 individually matched nonaffected controls and their respective first degree relatives (parents, sibs. and offspring) and spouses. The objective of this approach is to determine whether first degree relatives of patients have increased risk of developing the disease than relatives of controls. Twenty-two years after their establishment, the data of the registries were updated. The relatives of both patients and controls who developed either disease during the past twenty-two years have been identified and were recorded in the recurrence registry. All registry members who died during the same time were identified (by cross checking with the Guam death certificates) and the date of death and cause were recorded. The registry data are now ready for final analysis.

Major Findings: 1) Blood group frequencies immunoglobulin allotypes and dermatoglyphic frequencies of patients with ALS and PD of Guam were calculated and compared with those of non-affected Guamanians. The results indicated that none of the marker systems tested show any particular pattern of association in either patients or controls and therefore a genetic predisposition to either disorder, and the early identification of at risk individuals remains elusive. 2) Results of patient and control bone measurement and bone loss studies are discussed in project #Z01 AG 00022-05 CPB.

Significance to Bio-Medical Research and the Program of the Institute: The ultimate goal of this multidisciplinary program is not only to elucidate the etiology of Amyotrophic Lateral Sclerosis/Parkinsonism Dementia Complex of Guam, but also to provide a model for studying the genetic and familial aspects of other neurological diseases and dementias which are for the most part diseases of old age. It will also provide information on the effect of immobilization due to paralysis on bone mineral content (bone loss).

Proposed Course: To continue the analysis of the twenty-year follow-up data of the ALS/PD Patient Control Registry, and the Double Affected Registry. To complete the evaluation of bone loss data among patients with ALS/PD and non-affect Chamorros. And, to prepare reports for publication.

Publications:

Garruto, R.M., Plato, C.C. Myrionthopoulos, N.C., Schanfield, S.M. and Gajdusek, D.C.: Blood groups, immunoglobuline allotypes and dermatoglyphic features in patients with amyotrophic lateral sclerosis and Parkinsonism dementia of Guam. Am. J. Med. Genet. In Press.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 AG 00241-01 CPB

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Development of Statistical Methodology for the Analysis of BLSA Data

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	Larry J. Brant	Mathematical Statistician	CPB NIA

COOPERATING UNITS (if any)

Dr. David B. Duncan, Department of Biostatistics, School of Hygiene & Public Health, Johns Hopkins University

LAB/BRANCH
Gerontoloty Research Center, Clinical Physiology Branch

SECTION
Human Performance Section

INSTITUTE AND LOCATION
NIA, NIH, Baltimore, Maryland 21224

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:

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☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The theoretical development of statistical methodology is progressing in the areas of epidemiological models, multiple comparisons and survival analysis, each of which is applicable to longitudinal studies. The research utilizes Bayesian theory and various regression methods for prospective studies. The methodology created provides original contributions to experimental testing of treatments against a control or placebo, epidemiological study of disease states, survival or failure analysis of longitudinal data and other longitudinal observations representing growth and other physical changes of humans and animals. Accomplishments in the creative use of Bayesian theory in the area of multiple comparisons will fill a void in the established statistical armamentarium.

PHS-6040

Objectives: The aim of this project is to create and develop statistical methodology appropriate for the analysis of BLSA data.

Methods Employed: Empirical Bayesian statistical methods are used to solve various classes of multiple-comparisons and related simultaneous influence problems arising in many experimental situations including longitudinal studies. In addition, regression techniques for and related to time series concepts such as autoregression are used to model and compare the survival and/or failure patterns of different groups of longitudinal study subjects.

Major Findings: A binary variable multiple regression model has been applied to longitudinal data for study of the epidemiology of streptococcal disease in a population of 706 school children. Included in the development of the model was a means of calculating attributable risks for making comparisons. This idea has since been extended to the theoretically more complex multiple logistic model which has been used to study the problem of attrition among the BLSA participants.

The Bayesian solution for the experimental problem of comparing several treatments with a control has recently been completed. Besides solving this problem, the solution also provides important insight as to how these same methods might be extended to further classes of multiple-comparisons and related simultaneous inference problems. The new Bayesian, or "k-ratio" tests as they have been termed, give simultaneous rules with features which can be quite different from, but intuitively more acceptable than, those of the corresponding non-Bayesian α-level tests.

Proposed Course: Work is currently under way to develop a model appropriate for a life-table or survival analysis of longitudinal animal data collected on several groups of mice. Each of eleven groups has been given a carcinogen all starting at six weeks of age. Ten groups in turn have each been given one of ten treatments consisting of an anticarcinogen. One group acting as control has received no further treatment. All mice have been observed until death at which time they were examined for cancerous tumors. The types of cancer observed have been grouped into five classes.

The longitudinal nature of these data and the fact that the different groups of mice have started the experiment at different times over several years give these data several features in common with the BLSA data. The BLSA is, of course, a continuously ongoing study with many more complexities in terms of the amount and types of information collected. However, the longitudinal similarities of these mice data with the BLSA and the fewer possibilities of confounding variables, etc. makes this mice data set a good population to use in the development of new methods of longitudinal survival data analysis.

After the survival distribution of the mouse data has been appropriately modeled and analyzed, an important multiple comparisons problem arises. This consists not only of testing the efficacy of each of the ten anticarcinogen treatments against the control, it further includes the testing of the anticarcinogen effect on each of the five classes of cancer relative to the control. Currently, investigators with a problem of this type, are recommended to use Bonferroni inequalities because of the large number of simultaneous tests involved. However, the Bonferroni approach can fail to give significant differences in common situations in which many significant decisions would seem to be intuitively justified from the overall nature of the data outcome.

An important project which will remedy the losses of power in a Bonferroni approach without sacrificing its conservatism when this is required.

Publications:

Brant, L.J., Bender. T.R., and Marnell, R.W.: Factors affecting streto-coccal colonization among children in selected areas of Alaska. Public Health Reports. In press.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF** **INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 AG 00242-01 CPB

PERIOD COVERED

October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Female Sexuality, Menopause and Aging

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	Frances E. Purifoy	Staff Fellow	CPB	NIA
OTHER:	Jordan D. Tobin	Chief, Human Performance Section	CPB	NIA
	Clyde E. Martin	Sociologist	CPB	NIA

COOPERATING UNITS (if any)

Baltimore City Hospitals

LAB/BRANCH Gerontology Research Center, Clinical Physiology Branch

SECTION Human Performance Section

INSTITUTE AND LOCATION NIA, NIH, Baltimore, Maryland 21224

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☒ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A research project investigating both quantitative and qualitative measures of past and current sexual behavior was initiated in May, 1982 with the female participants of the Baltimore Longitudinal Study of Aging. Data is being obtained through the use of a semi-structured personal interview, conducted by the principal investigator. Plans are to obtain initial-interview data on all female participants; active in the program as of January, 1982 are 296 women, the majority of whom are married. New subjects will be interviewed as they are admitted to the program. Once established, this data base will provide descriptive cross-sectional information on variability in female sexuality by age and menopausal status, which can then be used in collaborative studies with other GRC scientists investigating various physiological and psychological parameters on the same population. It will also provide an initial-visit data base for longitudinal follow-up.

PHS-6040
(Rev. 2-81)

Project Description: Z01 AG 00242-01 CPB

Objectives: Major objectives include 1) To obtain initial-interview information regarding past and current sexual behavior on all currently active and newly admitted female participants of the BLSA 2) to assess the interrelationships of interview variables with each other and birth cohort, age and menopausal status, and ultimately, 3) to analyze the relationships between inter-individual and age-related variability in measures of sexuality and other physiological, psychological and sociological variables.

Methods employed: Data is being obtained by semi-structured personal interview conducted by the principal investigator, utilizing techniques similar to those presently used on male BLSA participants by Dr. Clyde E. Martin. Questions cover the following areas: current sexual behavior, past sexual behavior, sexual attitudes, and self-assessments of sexual interest and enjoyment as well as retrospective changes in sexuality. Responses are coded in cryptic form and kept strictly confidential.

All women who are active participants of the BLSA are interviewed. There are presently no exclusion criteria, except self-exclusion for anyone declining participation. Active in the BLSA as of January 1982 are 296 women with the following age distribution: ages 20-29, n=13; ages 30-39, n=46; ages 40-49, n=49; ages 50-59, n=53; ages 60-69, n=69; ages 70-79, n=47; ages 80, n=10. The majority are currently married; as of September, 1981, 20 were widowed, 20 divorced and 19 never-married. As of August 6, 1982, 39 women had been interviewed, and one had declined participation.

Major Findings: Since the study was just begun in May, 1982, sample size is still too small for adequate statistical inference. However, preliminary investigation of the data obtained thus far reveals a decrease in intercourse frequency in older as compared with younger participants, although enjoyment of sex is similar or may even be higher in the older age-groups. Much of the age-correlated decrease in sexual activity appears to be related to such situational factors as lack of a sexual partner, male impotence or marital dissatisfaction, although a great deal of variability in reported "desire" and a change in "desire" with age has already been noted. Expected cohort differences in premarital sexual behavior have also been noted; their relationship to current status will be analyzed when sample size becomes sufficient.

Significance to Biomedical Research: Although myths abound, little data now exists regarding the sexuality of older females. This investigation will thus provide valuable information for those in medicine and aging research on a group of well-educated healthy women on whom a great deal of information about other physiological and psychological information is available.

Proposed course: To continue initial interviews of all female participants, data reduction for computer storage, and statistical analyses when sample size becomes sufficiently large.

Publications: Chris C. Plato and F. E. Purifoy, 1982, "Age, Sex and Bilatera Variability in Cortical Bone Loss and Measurements of the Second Metacarpal" Growth 46: 100-112.

Report of the Planning and Extramural Affairs Program

Planning and Evaluation Office OPEA-1
Scientific Review Office OPEA-2
Program Analysis and Technical Information Office OPEA-2

OFFICE OF PLANNING AND EXTRAMURAL AFFAIRS

The responsibilities of the Office of Planning and Extramural Affairs (OPEA) encompass the full range of planning, evaluation, legislative, program analysis, and coordination activities relevant to the further development of the Institute's programs and policies. Over the past year, OPEA has made substantial progress in strengthening and streamlining the planning and evaluation, scientific review, and program analysis functions, improving the efficiency and management of OPEA operations, and developing collaborative relationships with other offices. The position of Deputy Associate Director for Planning and Extramural Affairs was established to provide assistance to the Associate Director in the numerous and varied activities of this office.

Planning and Evaluation Office

Concurrent with its involvement in the internal NIA planning and evaluation cycle and the coordination of NIA's participation in the central NIH and departmental planning, evaluation, and legislative processes, the Planning and Evaluation Office is completing the final steps of four major projects: (1) administrative and technical management of the development of a National Research Plan on Aging; (2) preparation of a comprehensive Inventory of Aging Research across the Department of Health and Human Services and eleven other Federal agencies; (3) evaluation of the main resource programs of NIA (cells and animals) and the Geriatric Medicine Academic Award; and (4) the development of a scientific data base for the Institute's Management Information System. Collectively, these projects represent a major NIA contribution to the planning, assessment, and evaluation of research on aging and provide a forum from which to address issues of national importance to aging research.

This office is also the central focus for activities that cut across NIA as well as NIH. They include: (1) provision of technical guidance and administrative support for the development and preparation of the response by the National Advisory Council on Aging (NACA) to the planning panel's report on the research plan, and (2) identification, coordination, and development of the overall long-term care research strategy as an NIA and trans-NIH issue. This second activity supports the Secretary of Health and Human Services Interdepartmental Work Group and the Public Health Service Work Group on Long-Term Care. The final report will provide the basis for a departmentwide legislative package on long-term care.

Several important activities that contribute to the effective and efficient management of the Institute's activities were completed and implemented by this office. They include:

- A referral agreement between NIA and NINCDS on SDAT, in cooperation with the Deputy Director.
- A Contract Policy Guidelines Manual that has been adopted by the Institute.

- A fully functioning Contract Advisory Committee that has put the planning and award of contracts on a regular schedule.

- A modified funding policy for research and training grants which addresses high- and low-program relevance determinations and type 2 competing renewals.

- Review procedures to be followed by the Council Work Group and full NACA for high- and low-program relevance recommendations and considerations of foreign grant applications.

- A formalized function for the Committee for Program Policy and Management to deal with policy and coordination issues at the program and office level within NIA.

- Implementation of extramural discussion seminars, in cooperation with the Deputy Director's office.

- A quality control system to review summary statements prepared by the Scientific Review Office to insure accuracy, consistency of format, and completeness of documentation.

- An eligibility review committee established to deal with responsiveness of the many support mechanisms used by NIA.

- Backup administrative and draft policy documents on aging research and the direction of the development of papers for the WHCoA.

- A background report on Federal aging research and training for the World Assembly on Aging.

Scientific Review Office

During the past year, the activities of this office have increased in scope, complexity, quantity of applications reviewed, and quality attained. The Aging Review Committee, the chartered Institute review body, has been increased from 15 to 22 members. All positions have either been filled or nominations have been made for them. This committee now reviews project grants (P01), small grants (R03), SERCAs (K01), Geriatric Medicine and Dentistry Academic Awards (K07), Clinical Investigator and NIA Academic Awards (K08), and National Research Service Awards (T32) and research contracts. Ad hoc reviews have until recently been conducted on a regularly scheduled basis for the Geriatric Medicine and Dentistry Academic Awards. This activity has now been modified to a simple annual review. In addition, ad hoc reviews are conducted when an applicant is also a member of the Aging Review Committee.

Program Analysis and Technical Information Office

During the past year, this office has continued to expand its data management and analysis activities and technical information services. It has maintained the ADRES system and allied data bases and provided the Institute with a wide variety of standard and ad hoc reports involving NIA projects.

It continued to monitor the MIS contract, which involves development of summaries of all NIA-funded projects from 1978 through 1981. These summaries are to be published in the third of a series of volumes describing aging research supported by this Institute. The development of scientific descriptors has been completed. They are now being assigned to NIA grants by the same contractor and will provide a method of information retrieval according to specific scientific content of each research project. Reporting from the Fiscal Ledger System has been expanded to include budget tables showing NIA commitments and the balance of uncommitted funds. Implementation of the Animal Models Inventory Data Base System has been completed with additional interactive input systems for principal investigator and transaction files. A small grants data base has been developed including both NIA administrative and initial review group data to be used for review purposes. Work was begun on an automated IRG Expenditure System including review and site visit costs with related travel, meeting, and consultant expenses. The NIA Council Orientation Handbook was revised and distributed. Responsibility was assumed for editing all summary statements generated by the Aging Review Committee and Institute *ad hoc* review groups. Responses were prepared for research inventory requests from other Institutes including population research, senile dementia, and cardiovascular and blood research. Finally, an inventory of slides and hard copy has been assembled for presentation at meetings by the Associate Director for Planning and Extramural Affairs.

Directions for Future Activities

OPEA has identified a number of new initiatives which should contribute significantly to strengthening the Institute's planning and evaluation, scientific review, and program analysis functions and to the further development of NIA.

- Linkage of the Management Information System (MIS), the Inventory of Aging Research in Federal Agencies, and the National Research Plan Information Data Base. OPEA proposes to design and implement a computerized system to link the MIS data base on research supported by NIA with both the National Research Plan subissues and issues and the Inventory of Aging Research supported by selected Federal agencies. Such a system would facilitate comprehensive, accurate, and rapid responses on important and developing research areas, thereby enhancing NIA's capabilities in a number of areas.

- Development of Mechanisms to Identify and Monitor Research Trends. OPEA plans to explore mechanisms designed to identify and analyze research trends of importance to the development of aging research. A

A system of information retrieval from bibliographic analysis combined with information from the Division of Research Grants' CRISP system should be developed to capture and cluster research activities in other Institutes that relate to NIA programs. These data will be analyzed to determine areas where NIA might intensify aging research efforts or develop collaborative approaches.

- Implementation of the National Research Plan on Aging. This Plan provides a vast array of information and data as well as related recommendations. OPEA proposes to develop an evaluation methodology for implementation of these recommendations, assess their feasibility (in collaboration with the extramural program staff), and examine methods for their conversion into a series of implementation plans for consideration by the Director, NIA. This activity is viewed as a long-term effort to be supported primarily by evaluation set-aside funds.

- Evaluation of the Geriatric Medicine Academic Award. The first phase of the Geriatric Medicine Academic Award (K07) evaluation has been completed. OPEA will now direct the data collection and analysis phase, the results of which will provide the basis for future program and policy decisions.

- Workshop on Senile Dementia of the Alzheimer's Type: Ethical Issues in Clinical Research. OPEA organized a workshop on this topic early in FY 1982. The product, in the form of a guide, will be completed and issued as a reference document for clinical investigation, particularly in SDAT.

- Modification of Council Review of Applications. A proposal is being developed on application review to develop alternative procedures for handling Council books of summary statements. Exploratory discussions are under way with other Institutes and the Office of Extramural Research and Training, NIH, and a task group had been formed to develop recommendations for new procedures.

- Consolidation of Scientific Review Records. Establishment of a microfiche filing system for review records is proposed to provide a archive-type resource, save space, and promote efficiency.

- Revision of Review Policies and Procedures. Consolidated policies and guidelines for scientific review will be developed to insure uniform and consistent review procedures.

- Implementation of the Scientific Data Base. The new scientific data base will be brought to current status (all projects through those currently active will be coded), and the retrieval system will be implemented and refined. In addition, the NIH data base (CRISP) will be augmented with aging terminology to provide access to aging research conducted by other Institutes.

- Development of Systems Linkages. The Fiscal Ledger System will be interfaced with the ADRES system through the existing report formats so that the most current funding will be available on many types of ADRES reports. The Animal Models Modeling and Projection System will be linked to the Animal Models Inventory System to allow prediction of future needs based on current census and predicted depletion factors.

- Inventory Development and Retrieval. An inventory of health promotion and disease prevention research supported by the Institute will be developed. Assistance will also be provided for the standardization of reporting techniques for NIH prevention-related research. A system will be planned and developed for the management and retrieval of the Government-wide Inventory of Aging Research.

o Analysis of the NIA Training Effort. A statistical package of NIA training data will be developed.

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